Hepatitis C Agents
Therapeutic Class Review (TCR)

June 1, 2022

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FDA-APPROVED INDICATIONS

Drug	Mfr	FDA-Approved Indications
Interferon		
peginterferon alfa-2a (Pegasys®)[1]	Genentech, zr pharma& GmbH	Chronic hepatitis C (CHC) ▪ Treatment of adults with CHC as part of a combination regimen with other hepatitis C virus antiviral drugs in patients ≥ 5 years old with compensated liver disease ▪ Monotherapy is not recommended unless a patient has a contraindication to, or significant intolerance of, other HCV antiviral drugs Chronic hepatitis B (CHB) ▪ Treatment of HBeAg-positive and HBeAg-negative chronic hepatitis B in adults with compensated liver disease and evidence of viral replication and liver inflammation ▪ Treatment of non-cirrhotic pediatric patients ≥ 3 years old with HBeAg-positive CHB and evidence of viral replication and elevations in serum alanine aminotransferase
Ribavirin		
ribavirin capsule[2]	generic	Chronic hepatitis C ▪ In combination with interferon alfa-2b (pegylated[ł] or non-pegylated) in patients (≥ 3 years of age) with compensated liver disease Ribavirin must not be used as monotherapy; Patients with the following characteristics are less likely to benefit from retreatment after failing a course of therapy: previous nonresponse, previous peginterferon treatment, significant bridging fibrosis or cirrhosis, and genotype 1 infection; No safety and efficacy data are available for treatment of longer than 1 year
ribavirin tablet[3]	generic	Chronic hepatitis C ▪ In combination with peginterferon alfa-2a (Pegasys) in patients ≥ 5 years of age with compensated liver disease and have not been previously treated with interferon alfa ▪ Includes patients with histological evidence of cirrhosis (Child-Pugh A) ▪ Includes adult patients with clinically stable human immunodeficiency virus (HIV) disease and CD4 count > 100 cells/mm^2 Ribavirin must not be used as monotherapy; Safety and efficacy have not been demonstrated with treatment longer than 48 weeks; Safety and efficacy have not been established in liver or other organ transplant recipients, patients with decompensated liver disease, or previous non-responders to interferon therapy

ł Pegylated interferon alfa-2b (PEGIntron) was discontinued by the manufacturer in 2016.

FDA-Approved Indications (continued)

Drug	Mfr	FDA-Approved Indications
Oral NS5B Polymerase Inhibitor		
sofosbuvir (Sovaldi®)[4]	Gilead	Chronic hepatitis C genotype 1, 2, 3, or 4 in adults ▪ As a component of a combination antiviral treatment regimen ▪ Without cirrhosis or with compensated cirrhosis Chronic hepatitis C genotypes 2 or 3 in pediatric patients (≥ 3 years of age) ▪ In combination with ribavirin ▪ Without cirrhosis or with compensated cirrhosis
Oral Combination Products		
elbasvir/grazoprevir (Zepatier®)[5]	Merck Sharpe & Dohme	Chronic hepatitis C genotype 1 or 4 in adult and pediatric patients ≥ 12 years of age or weighing ≥ 30 kg ▪ Co-formulated fixed-dose tablet of elbasvir (an NS5A inhibitor) and grazoprevir (an NS3/4A protease inhibitor) ▪ Indicated for use with or without ribavirin ▪ Testing for NS5A resistance-associated polymorphisms needed for genotype 1a ▪ Without cirrhosis or with compensated cirrhosis
glecaprevir/ pibrentasvir (Mavyret®)[6]	Abbvie	Chronic hepatitis C genotype 1, 2, 3, 4, 5, or 6 infection in adults and pediatric patients (≥ 3 years of age) ▪ Mavyret includes a combination of glecaprevir (an NS3/4A protease inhibitor) and pibrentasvir (an NS5A inhibitor) ▪ Indicated for use without ribavirin ▪ Without cirrhosis or with compensated cirrhosis Indicated for use in treatment-experienced genotype 1 patients with prior regimen containing either an HCV NS5A inhibitor or an HCV NS3/4A PI, but not both
ledipasvir/sofosbuvir (Harvoni®)[7]	generic*, Gilead	Chronic hepatitis C genotype 1, 4, 5, or 6 in adults and pediatric patients (≥ 3 years of age) ▪ Without cirrhosis or with compensated cirrhosis ▪ Co-formulated fixed-dose tablet of ledipasvir (an NS5A inhibitor) and sofosbuvir (an NS5B Inhibitor) ▪ Indicated for use without ribavirin Chronic hepatitis C genotype 1 in adults and pediatric patients (≥ 3 years of age) ▪ With decompensated cirrhosis, in combination with ribavirin Chronic hepatitis C genotypes 1 or 4 in adults and pediatric patients (≥ 3 years of age) who are liver transplant recipients without cirrhosis or with compensated cirrhosis, in combination with ribavirin
ombitasvir/ paritaprevir/ritonavir + dasabuvir (Viekira Pak®)[8]	Abbvie	Chronic hepatitis C genotype 1 in adults ▪ Viekira Pak includes the combination of ombitasvir (an NS5A inhibitor), paritaprevir (a protease inhibitor), ritonavir (a potent CYP3A inhibitor to pharmacologically boost paritaprevir), and dasabuvir (an NS5B polymerase inhibitor) Indicated for use with or without ribavirin, including in those with compensated cirrhosis

* Authorized generic

FDA-Approved Indications (continued)

Drug	Mfr	FDA-Approved Indications
Oral Combination Products *(continued)*		
sofosbuvir/velpatasvir (Epclusa)[9]	generic*, Gilead	Chronic hepatitis C genotype 1, 2, 3, 4, 5, or 6 infection in adults and pediatric patients ≥ 3 years of age ▪ Epclusa includes a combination of sofosbuvir (an NS5B polymerase inhibitor) and velpatasvir (an NS5A inhibitor) ▪ Without cirrhosis or with compensated cirrhosis ▪ With decompensated cirrhosis, in combination with ribavirin Treatment-naïve or treatment-experienced liver transplant recipients without cirrhosis or with compensated cirrhosis
sofosbuvir/velpatasvir/ voxilaprevir (Vosevi™)[10]	Gilead	Chronic hepatitis C genotype 1, 2, 3, 4, 5, or 6 infection in adults ▪ Vosevi includes a combination of sofosbuvir (an NS5B polymerase inhibitor), velpatasvir (an NS5A inhibitor), and voxilaprevir (an HCV NS3/4A protease inhibitor) ▪ Treatment-experienced genotype 1, 2, 3, 4, 5, and 6 patients with prior regimen containing an HCV NS5A inhibitor ▪ Treatment-experienced genotype 1a or 3 patients with prior regimen containing sofosbuvir without an NS5A inhibitor ▪ Indicated for use without ribavirin ▪ Without cirrhosis or with compensated cirrhosis Additional benefit over sofosbuvir/velpatasvir was not shown in adults with genotype 1b, 2, 4, 5, or 6 infection previously treated with sofosbuvir without a NS5A inhibitor

* Authorized generic

OVERVIEW

Hepatitis C virus (HCV) infection is the most common chronic blood-borne infection in the United States (US). In approximately 15% to 25% of patients who become infected with hepatitis C, the virus is eliminated during the acute phase of the infection by T cell-mediated antiviral mechanisms; however, in the other 75% to 85% of patients, HCV is chronic and may persist for decades without treatment.[11] An estimated 23,000 to 46,000 children in the US have HCV.[12] The seroprevalence is approximately 0.2% for children ages 6 to 11 years and 0.4% for those 12 to 19 years of age.[13] New HCV infections in children are primarily the result of perinatal transmission.[14] Approximately 2.4 million people in the US are chronically infected, although it is estimated that nearly 51% of these people may be unaware of their infection due to the insidious progression of the disease.[15] HCV accounts for 40% of chronic liver disease in the US. In patients with chronic HCV infection followed for 20 years, disease progression to cirrhosis occurs in about 5% to 25%. The rate of hepatocellular carcinoma in HCV infected persons ranges from 1% to 3% over 30 years.[16] HCV infection is the most common reason for liver transplantation and results in an approximate 14,000 deaths per year in the US, reported in 2019.[17]

Transmission of HCV occurs primarily through percutaneous exposure to infected blood. The most important risk for HCV infection is injection-drug use, which accounts for at least 60% of acute HCV infections in the US. Other modes of transmission include mother-to-infant, receiving a blood or organ donation prior to 1992, occupational exposures, chronic hemodialysis, and contaminated devices shared for non-injection drug use, such as intranasal illicit drug use. Sexual transmission also occurs but generally seems to be inefficient except among human immunodeficiency virus (HIV)-infected men who

have unprotected sex with men. Other risk factors include incarceration and receiving a tattoo in an unregulated setting. It is estimated that up to 39% of incarcerated persons in the North America are anti-HCV positive.[18]

Identification of persons infected with HCV is an important medical goal due to the proven benefits of care and treatment in reducing the risk of hepatocellular carcinoma and all-cause mortality. In addition, there is a potential public health benefit by reducing transmission through early treatment, viral clearance, and reduced risk behaviors.[19] The Centers for Disease Control and Prevention (CDC) estimates that baby boomers born from 1945 to 1965 account for 75% of all HCV infections.[20] In August 2012, the CDC issued updated guidelines for HCV testing recommending all persons born from 1945 to 1965 (baby boomers) receive a 1-time testing for HCV without prior ascertainment of risk-factor information. In 2020, the United States Preventive Services Task Force (USPSTF) expanded the population for a 1-time screening to asymptomatic adults 18 to 79 years of age.[21] Similarly, joint guidelines from the American Association for Liver Diseases (AASLD) and the Infectious Disease Society of America (IDSA) recommend a 1-time, routine, opt-out HCV testing for anyone 18 years and older.[22] Annual testing is recommended for injection drug users, HIV-infected men who have unprotected sex with men, and men who have sex with men taking pre-exposure prophylaxis (PrEP). In addition, the CDC recommends periodically testing other persons based on exposures, behaviors, and conditions that increase the risk for HCV infection.[23] Periodic HCV testing is recommended for persons who inject drugs and share needles and those receiving hemodialysis. Periodic testing should also be offered to other persons with ongoing risk factors for exposure to HCV. In addition, all infected carriers of HCV should receive a brief alcohol screening and intervention as clinically indicated, followed by referral to appropriate care and treatment services for HCV infection and related conditions.

Initial HCV testing is designed to detect the presence of HCV antibody (anti-HCV).[24] The Food and Drug Administration (FDA)-approved tests include laboratory-based assays and a point-of-care assay that has a sensitivity and specificity similar to the FDA-approved laboratory-based HCV antibody assays. A positive test result for anti-HCV indicates the patient has a current active HCV infection (acute or chronic), the patient had a past infection that has resolved, or it is a false-positive test result. Therefore, a confirmatory test to detect the presence of HCV RNA is necessary prior to initiating treatment. Assays for HCV RNA are the most sensitive tests for HCV infection and represent the gold standard in establishing a diagnosis of HCV. HCV RNA is reported as international units (IUs) per milliliter; these quantitative assays allow detection of HCV RNA with a sensitivity as low as 5 IU/mL. HCV RNA can be detected within a few days of exposure to HCV, well before the presence of anti-HCV, and tends to persist for the duration of HCV infection. Due to the diversity and the high mutation rate of HCV, immunity does not appear to develop after HCV infection. Testing of persons with suspected reinfection after previous spontaneous or treatment-related viral clearance should be done with initial HCV-RNA testing because an anti-HCV test is expected to be positive in this cohort of patients.[25] Prior to the initiation of HCV therapy, quantitative HCV RNA testing is also necessary to document the baseline level of viral load, as well as testing to determine the HCV genotype. Knowledge of the baseline viral load is utilized to measure the degree of viral decline after initiation of treatment; this is important for regimens requiring response-guided treatment decisions. Knowledge of the HCV genotype is important for selecting the most appropriate treatment regimen.

The standard measure of virological cure for hepatitis C treatment is the sustained virologic response (SVR).[26] SVR12 is defined as undetectable serum HCV RNA 12 weeks after discontinuation of treatment.

When suppression of viral replication has been maintained for 12 weeks after treatment, the patient can be considered cured of chronic hepatitis C (CHC).[27] Prior to the approval of simeprevir (Olysio) and sofosbuvir (Sovaldi), all HCV therapies approved by the FDA had based efficacy assessment by the proportion of patients attaining SVR24 in the phase 3 confirmatory studies.[28] However, SVR12 and SVR24 measurements have been found to be concordant, and SVR12 is now considered suitable as a primary endpoint for regulatory approval.

There are 6 HCV genotypes and more than 50 subtypes. The distribution of HCV genotypes varies across the world. Genotype 1 is the most common worldwide and accounts for about 70% to 75% of US infections; among African Americans, the frequency of genotype 1 is even higher at an estimated 90%.[29] In the US, genotype 1a and 1b represent about 75% and 25% of genotype 1 cases, respectively. Genotypes 2 and 3 account for the majority of the other approximate 25% to 30% HCV infections in the US. Genotype 4 predominates in Egypt, genotype 5 is localized to South Africa, and genotype 6 to Hong Kong and Southeast Asia.[30] Hepatitis C viral genotype is an important factor in selecting the optimal treatment planning, dictating drug selection, dose, and duration of treatment.

Historically, genotype 1 patients were treated with interferon monotherapy, which resulted in SVR rates of only 10% to 20%.[31] With the addition of ribavirin, dual therapy of peginterferon + ribavirin (PEG/RBV) therapy achieved SVR rates of 40% to 50% in this genotype. The first generation oral protease inhibitors, boceprevir (Victrelis®) and telaprevir (Incivek®), were introduced in 2011 representing the initial direct-acting antiviral agents (DAA) which act directly to disrupt the replication of the hepatitis C virus.[32] Their approval ushered in triple combination therapy consisting of an oral protease inhibitor, peginterferon, and ribavirin. Because of the triple combination therapy, improved rates of SVR for genotype 1 treatment-naïve patients of approximately 60% to 80% were reported.[33,34] Boceprevir (Victrelis) and telaprevir (Incivek) have since been discontinued. In 2013, simeprevir (Olysio®) and sofosbuvir (Sovaldi) were approved, although simeprevir, a second-generation protease inhibitor, has since been discontinued. Sofosbuvir was the first in a new class of DAAs classified as an HCV nucleotide analog NS5B polymerase inhibitor approved in combination with peginterferon and ribavirin or with ribavirin alone, depending on the genotype. The combination of sofosbuvir with ribavirin was the first FDA-approved all-oral regimen for the treatment of HCV. By eliminating interferon, numerous adverse effects associated with interferon therapy are avoided. The resulting "all oral interferon-free" regimen is, therefore, more favorable. Beginning with sofosbuvir, and continuing with subsequently approved treatments, SVR rates as high as 90% or greater (depending on genotype and prior treatment experience) were demonstrated in clinical trials.[35] In 2014, there were multiple rulings by the FDA that brought about new therapies for the treatment of hepatitis C and new indications for previously approved medications. In October 2014, the combination tablet of ledipasvir/sofosbuvir (Harvoni) received initial approval for genotype 1, and expanded approval in November 2015 for genotypes 4, 5, and 6. Ledipasvir is the first in a new class of DAAs classified as an HCV NS5A inhibitor available as a fixed-dose combination with sofosbuvir taken as a single tablet once daily. The combination ombitasvir/paritaprevir/ritonavir + dasabuvir (Viekira Pak) was approved in December 2014 for use in genotype 1 with an extended-release formulation (Viekira XR) approved in July 2016. Viekira XR has since been removed from the market. This combination includes an NS5A inhibitor (ombitasvir), an NS3A/4A protease inhibitor (paritaprevir), a non-nucleoside NS5B polymerase inhibitor (dasabuvir), and a CYP3A inhibitor (ritonavir) to boost paritaprevir pharmacologically providing increased plasma concentrations. A similar combination, ombitasvir/paritaprevir/ritonavir (Technivie®), was approved in 2015 for the treatment of genotype 4 in combination with ribavirin but has also since been discontinued. Daclatasvir (Daklinza®), an NS5A

inhibitor, was also approved in 2015. It was indicated for use with sofosbuvir (with or without ribavirin) for the treatment of HCV genotypes 1 or 3, but SVR rates were reduced in genotype 3 patients with cirrhosis. Notably, however, Bristol-Myers Squibb ceased distribution of Daklinza (daclatasvir) effective June 2019. In January 2016, the fixed-dose combination of elbasvir/grazoprevir (Zepatier), an NS5A inhibitor and an NS3/4A protease inhibitor, was approved for use with or without ribavirin for HCV genotypes 1 or 4. The first pangenotypic combination therapy effective in the treatment of all 6 genotypes, sofosbuvir/velpatasvir (Epclusa), was approved in June 2016. In July 2017, sofosbuvir/velpatasvir/voxilaprevir (Vosevi), a fixed-dose combination of an NS5B polymerase inhibitor, an NS5A inhibitor, and an NS3/4A protease inhibitor was approved representing the first pangenotypic therapy indicated specifically for use in treatment-experienced patients with prior therapy containing an NS5A inhibitor or genotype 1a or 3 infected patients who were previously treated with sofosbuvir without an NS5A inhibitor. In August 2017, glecaprevir/pibrentasvir (Mavyret), a combination of an NS3/4A protease inhibitor and an NS5A inhibitor, was approved as a fixed-dose pangenotypic therapy indicated for use in treatment-naïve patients and genotype 1 treatment-experienced patients with prior therapy with an NS5A inhibitor or an NS3/4A protease inhibitor, but not both.

The joint guidelines from the AASLD/IDSA Recommendations for Testing, Managing, and Treating Hepatitis C continue to be updated with the advent of new therapies and other developments in care.[36] One important section of the updated AASLD/IDSA recommendations includes guidance on "When and in Whom to Initiate Therapy" addressing the limitations of feasibility associated with treating all patients. The goal of treatment of HCV-infected persons is to reduce all-cause mortality and liver-related health adverse consequences, including end-stage liver disease and hepatocellular carcinoma, by the achievement of virologic cure, as evidenced by an SVR. Patients cured of their HCV infection experience numerous health benefits, including a decrease in liver inflammation and a reduction in the rate of progression of liver fibrosis and mortality from severe extrahepatic manifestations, such as cryoglobulinemic vasculitis, a condition affecting 10% to 15% of HCV-infected patients. While the guidelines initially supported prioritizing treatment to patients who would experience the most benefit from receiving treatment and patients whose treatment would have the greatest impact on reducing further HCV transmission, more recent revisions support treatment for all patients with chronic HCV. The guidelines note a few exceptions to this treat-all approach: patients with a short life expectancy unlikely to be remediated by HCV treatment, transplantation, or other directed therapy.

With regard to treatment, the guidelines define recommended regimens (favored for most patients) and alternative regimens (optimal in a particular subset of patients). Any regimens that are not recommended are clearly inferior or harmful treatment options. Some of the recommended and alternative regimens outlined in the guidelines, as well as therapy recommendations for special populations, are based on unpublished data and may go beyond the scope of the current FDA-approved labeling for these products. The guidelines also provide treatment recommendations for patients who have failed previous therapy (partial or null responders), patients coinfected with HIV, patients with renal impairment, patients with hepatic impairment, and patients who develop recurrent HCV post liver transplant. These populations and the applicable guideline recommendations are discussed in the "Special Populations" section of this review. The guidelines also include simplified regimens that can be used in patients unless they are treatment experienced, have decompensated cirrhosis and/or end stage renal disease, are HIV or HBsAg positive, are pregnant, have known or suspected hepatocellular cancer, or prior liver transplant.

Summary of the AASLD/IDSA HCV Guidelines Recommendations[37]

Any Genotype

Treatment Experience	Treatment	Duration (weeks)	Rating
Any Genotype - Simplified Treatments			
Treatment-Naïve	Patients **without** cirrhosis: ▪ glecaprevir/pibrentasvir ▪ sofosbuvir/velpatasvir Patients **with compensated** cirrhosis: ▪ glecaprevir/pibrentasvir ▪ sofosbuvir/velpatasvir (all genotypes except GT 3 with Y93H present)	 8 12 8 12	--
Any Genotype			
Treatment-Experienced (previous sofosbuvir/ velpatasvir/ voxilaprevir treatment failure)	Patients **with or without** compensated cirrhosis: ▪ glecaprevir/pibrentasvir + sofosbuvir + weight-based-RBV ▪ sofosbuvir/velpatasvir/voxilaprevir + weight-based RBV	 16 24	 Class IIa, Level B Class IIa, Level B
Treatment-Experienced (previous failure of sofosbuvir-based regimen)	Patients **without** cirrhosis: ▪ sofosbuvir/velpatasvir/voxilaprevir Patients **with compensated** cirrhosis: ▪ sofosbuvir/velpatasvir/voxilaprevir (for genotype 3 and cirrhosis; add RBV)	 12 12	 Class I, Level A Class I, Level A
Treatment-Experienced (previous failure of elbasvir/grazoprevir)	Patients **with or without** cirrhosis: ▪ sofosbuvir/velpatasvir/voxilaprevir	 12	 Class I, Level A
Treatment-Experienced (previous glecaprevir/ pibrentasvir treatment failure)	Patients **with or without** compensated cirrhosis: ▪ glecaprevir/pibrentasvir + sofosbuvir + weight-based RBV ▪ sofosbuvir/velpatasvir/voxilaprevir ▪ sofosbuvir/velpatasvir/voxilaprevir + weight-based RBV (patients with compensated cirrhosis)	 16 12 12	 Class IIa, Level B Class IIa, Level B Class IIa, Level C
Any Genotype – Alternative Treatments			
Treatment-Experienced (previous failure of sofosbuvir-based regimen)	Patients **with or without** compensated cirrhosis: ▪ glecaprevir/pibrentasvir (except for NS3/4 PI inclusive combination DAA regimen failures) Not for genotype 3 infection with sofosbuvir/NS5A inhibitor or for those with prior exposure to an NS5A inhibitor + NS3/4 PI regimen	 16	 Class I, Level A

Genotype 1

Treatment Experience	Treatment	Duration (weeks)	Rating
Genotype 1a – Recommended Treatments			
Treatment-Naïve	Patients **without** cirrhosis:		
	▪ glecaprevir/pibrentasvir	8	Class I, Level A
	▪ ledipasvir/sofosbuvir	12	Class I, Level A
	▪ ledipasvir/sofosbuvir (HIV-uninfected and HCV RNA level is < 6 million IU/mL)	8	Class I, Level B
	▪ sofosbuvir/velpatasvir	12	Class I, Level A
	Patients **with compensated** cirrhosis:	12	Class I, Level A
	▪ ledipasvir/sofosbuvir	12	Class I, Level A
	▪ sofosbuvir/velpatasvir	8	Class I, Level B
	▪ glecaprevir/pibrentasvir		
Genotype 1a – Alternative Treatments			
Treatment-Naïve	Patients **without** cirrhosis:		
	▪ elbasvir/grazoprevir	12	Class I, Level A
Genotype 1b – Recommended Treatments			
Treatment-Naïve	Patients **without** cirrhosis:		
	▪ elbasvir/grazoprevir	12	Class I, Level A
	▪ glecaprevir/pibrentasvir	8	Class I, Level A
	▪ ledipasvir/sofosbuvir	12	Class I, Level A
	▪ ledipasvir/sofosbuvir (HIV-uninfected, and HCV RNA level is < 6 million IU/mL)	8	Class I, Level B
	▪ sofosbuvir/velpatasvir	12	Class I, Level A
	Patients **with compensated** cirrhosis:		
	▪ elbasvir/grazoprevir	12	Class I, Level A
	▪ ledipasvir/sofosbuvir	12	Class I, Level A
	▪ sofosbuvir/velpatasvir	12	Class I, Level A
	▪ glecaprevir/pibrentasvir (HIV/HCV-coinfected)	8 (12)	Class I, Level B
Genotype 1 (regardless of subtype, unless noted) – Recommended Treatments			
Treatment-Experienced (previous failure of any NS5A inhibitor excluding glecaprevir/pibrentasvir failure)	Patients **without cirrhosis or with compensated** cirrhosis:		
	▪ sofosbuvir/velpatasvir/voxilaprevir	12	Class I, Level A

Genotype 2

Treatment Experience	Treatment	Duration (weeks)	Rating
Genotype 2 – Recommended Treatments			
Treatment-Naïve	Patients **without** cirrhosis:		
	▪ glecaprevir/pibrentasvir	8	Class I, Level A
	▪ sofosbuvir/velpatasvir	12	Class I, Level A
	Patients **with compensated** cirrhosis:		
	▪ sofosbuvir/velpatasvir	12	Class I, Level A
	▪ glecaprevir/pibrentasvir (HIV/HCV-coinfected)	8 (12)	Class I, Level B

Genotype 3

Treatment Experience	Treatment	Duration (weeks)	Rating
Genotype 3 – Recommended Treatments			
Treatment-Naïve	Patients **without** cirrhosis:		
	▪ glecaprevir/pibrentasvir	8	Class I, Level A
	▪ sofosbuvir/velpatasvir	12	Class I, Level A
	Patients **with compensated** cirrhosis:		
	▪ sofosbuvir/velpatasvir (without Y93H present)	12	Class I, Level A
	▪ glecaprevir/pibrentasvir (HIV/HCV-coinfected)	8 (12)	Class I, Level B
Genotype 3 – Alternative Treatments			
Treatment-Naïve	Patients **with compensated** cirrhosis:		
	▪ sofosbuvir/velpatasvir/voxilaprevir (when Y93H present)	12	Class IIa, Level B
	▪ sofosbuvir/velpatasvir ± weight-based RBV (when Y93H present)	12	Class IIa, Level A

Genotype 4

Treatment Experience	Treatment	Duration (weeks)	Rating
Genotype 4 – Recommended Treatments			
Treatment-Naïve	Patients **without** cirrhosis:		
	▪ glecaprevir/pibrentasvir	8	Class I, Level A
	▪ sofosbuvir/velpatasvir	12	Class I, Level A
	▪ ledipasvir/sofosbuvir	12	Class I, Level A
	▪ elbasvir/grazoprevir	12	Class I, Level A
	Patients **with compensated** cirrhosis:		
	▪ sofosbuvir/velpatasvir	12	Class I, Level A
	▪ glecaprevir/pibrentasvir (HIV/HCV-coinfected)	8 (12)	Class I, Level B
	▪ elbasvir/grazoprevir	12	Class IIa, Level B
	▪ ledipasvir/sofosbuvir	12	Class IIa, Level B

Genotypes 5 and 6

Few data are available to help guide decision making in patients with genotypes 5 or 6; however, these genotypes are uncommon in the US.

Treatment Experience	Treatment	Duration (weeks)	Rating
Genotype 5/6 – Recommended Treatments			
Treatment-Naïve	Patients **without** cirrhosis:		
	▪ glecaprevir/pibrentasvir (HIV/HCV-coinfected)	8 (12)	Class I, Level A
	▪ sofosbuvir/velpatasvir	12	Class I, Level B
	▪ ledipasvir/sofosbuvir (not recommended for genotype 6e)	12	Class IIa, Level B
	Patients **with compensated** cirrhosis:		
	▪ glecaprevir/pibrentasvir (HIV/HCV-coinfected)	8 (12)	Class I, Level B
	▪ sofosbuvir/velpatasvir	12	Class I, Level B
	▪ ledipasvir/sofosbuvir (not recommended for genotype 6e)	12	Class IIa, Level B

PEG-IFN = peginterferon; RAV = resistance-associated variants; RBV = ribavirin

Grading System Used to Rate the Level of the Evidence and Strength of the Recommendation for Each Recommendation

Classification

- **Class I –** Conditions for which there is evidence and/or general agreement that a given diagnostic evaluation, procedure, or treatment is beneficial, useful, and effective
- **Class II –** Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness and efficacy of a diagnostic evaluation, procedure, or treatment
- **Class IIa –** Weight of evidence and/or opinion is in favor of usefulness and efficacy
- **Class IIb –** Usefulness and efficacy are less well established by evidence and/or opinion
- **Class III –** Conditions for which there is evidence and/or general agreement that a diagnostic evaluation, procedure, or treatment is not useful and effective or if it in some cases may be harmful

Level of Evidence

- **Level A –** Data derived from multiple randomized clinical trials, meta-analyses, or equivalent
- **Level B –** Data derived from a single randomized trial, nonrandomized studies, or equivalent
- **Level C –** Consensus opinion of experts, case studies, or standard of care

PHARMACOLOGY[38,39,40,41,42,43,44,45,46,47,48,49,50,51,52]

Interferons

Most interferon compounds are naturally occurring small proteins and glycoproteins produced and secreted by cells in response to viral infections and other synthetic or biological inducers. Peginterferons are produced by binding the large inert polyethylene glycol moiety to interferon molecules, thus decreasing renal clearance, altering metabolism, and increasing the half-life of the interferon molecule.[53] Because of their long half-lives, peginterferons can be administered subcutaneously (SC) once weekly.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Once bound to the cell membrane, interferons initiate a complex sequence of intracellular events, including the induction of certain enzymes, suppression of cell proliferation, immunomodulating activities, such as enhancement of the phagocytic activity of macrophages and augmentation of the

specific cytotoxicity of lymphocytes for target cells, and inhibition of virus replication in virus-infected cells.

Ribavirin

Ribavirin is a nucleoside analog with antiviral activity. Ribavirin is phosphorylated intracellularly to the triphosphate metabolite. Once phosphorylated, ribavirin disrupts cellular purine metabolism by inhibiting inosine monophosphate dehydrogenase, which leads to a decrease in guanosine triphosphate. Ribavirin may also act as a potent RNA virus mutagen and increase the mutation rate of RNA viruses. Typically, RNA viruses have a high mutation rate that enables the virus to evolve rapidly and escape host immune mechanisms; however, the high mutation rate is also associated with the production of nonviable virions. Ribavirin monotherapy is not effective for the treatment of chronic hepatitis C, and ribavirin should not be used alone for this indication.[54] The mechanism of inhibition of HCV RNA by combination therapy with interferon alfa and ribavirin has not been established.

Protease Inhibitors

DAAs are newer medications approved for the treatment of HCV. One group of DAAs are classified as protease inhibitors and consist of glecaprevir (available as part of Mavyret), grazoprevir (available as part of Zepatier), paritaprevir (available as part of Viekira Pak), and voxilaprevir (available as part of Vosevi). These agents inhibit hepatitis C NS3/4A protease, which is essential for replication of the virus.

NS5B Inhibitors

Sofosbuvir (available as the single agent, Sovaldi, and as part of Epclusa, Harvoni, and Vosevi) and dasabuvir (available as part of Viekira Pak) represent another group of DAAs classified as a NS5B polymerase inhibitors. These agents inhibit the HCV NS5B RNA-dependent RNA polymerase, which is required for viral replication. Sofosbuvir is a nucleotide prodrug that undergoes intracellular metabolism to form the pharmacologically active uridine analog triphosphate (GS-461203), which can be incorporated into HCV RNA by the NS5B polymerase and acts as a chain terminator. Dasabuvir targets the palm domain of the NS5B polymerase and is referred to as a non-nucleoside NS5B-palm polymerase inhibitor.

NS5A Inhibitors

Another group of DAAs are the NS5A inhibitors and consist of elbasvir (available as part of Zepatier), ledipasvir (co-formulated with sofosbuvir and available as Harvoni), ombitasvir (available as part of Viekira Pak), pibrentasvir (co-formulated with glecaprevir and available as Mavyret), and velpatasvir (co-formulated with sofosbuvir and available as Epclusa and Vosevi). These agents inhibit the HCV NS5A, which is essential for viral RNA replication and virion assembly.

Ritonavir

Ritonavir (available as part of Viekira Pak) is not active against the hepatitis C virus; it is a CYP3A4 inhibitor used to increase plasma concentrations of paritaprevir.

PHARMACOKINETICS[55,56,57,58,59,60,61,62,63,64,65,66,67,68,69]

Interferons

The half-life of interferon alfa is approximately 5 to 8 hours. Dosing 3 times weekly results in undetectable blood levels of interferon during the remaining 4 days of the week. Pegylation of interferon has extended the mean steady-state half-life to 160 hours for peginterferon alfa-2a (Pegasys), allowing this agent to be given once weekly. The half-life of peginterferon alfa-2a accumulates over time with multiple dosing. In patients with end-stage renal disease undergoing hemodialysis, there is a 25% to 45% reduction in clearance of peginterferon alfa-2a. Dose reduction of peginterferon is necessary for patients with moderate renal impairment.

Ribavirin

The terminal half-life of ribavirin (generics for Copegus) with multiple dosing is 120 to 170 hours. The half-life of ribavirin (generics for Rebetol) has been reported as 298 hours. Ribavirin is metabolized by phosphorylation and degradation prior to being renally eliminated.

Elbasvir/grazoprevir

Elbasvir and grazoprevir (Zepatier) reach mean peak concentration within 3 hours and 2 hours, respectively, following oral administration. Both components are highly protein-bound and undergo oxidative metabolism, primarily by CYP3A enzymes, with excretion occurring predominantly through the feces (greater than 90%).

Glecaprevir/pibrentasvir

Glecaprevir and pibrentasvir (Mavyret) reach mean peak concentration approximately 5 hours after oral administration. The pharmacokinetics of both components are significantly altered by meals and should be administered with food. Both components are highly protein bound. Pibrentasvir is metabolized through the biliary-fecal route with approximately 97% of the drug excreted in the feces. Glecaprevir is primarily metabolized via the biliary-fecal route, with a secondary metabolism by CYP3A4, and approximately 92% of the drug is excreted in the feces.

Ledipasvir

Ledipasvir reaches its mean peak concentration approximately 4 to 4.5 hours after oral administration. The pharmacokinetics of ledipasvir is not significantly altered by meals and can be administered without regard to food. There was no detectable metabolism of ledipasvir by cytochrome P450 isoenzymes CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4. Ledipasvir is eliminated in the feces primarily unchanged. Exposure of ledipasvir in pediatric patients ≥ 3 years of age is similar to that observed in adults.

Ombitasvir/paritaprevir/ritonavir and dasabuvir

Ombitasvir/paritaprevir/ritonavir + dasabuvir (Viekira Pak) reaches its mean peak concentration approximately 4 to 5 hours after oral administration. The absolute bioavailability of dasabuvir is approximately 70%, and when administered with ritonavir, the absolute bioavailability of ombitasvir and paritaprevir are approximately 48.1% and 52.6%, respectively. Ombitasvir/paritaprevir/ritonavir + dasabuvir should always be administered with a meal as the mean AUC is increased under fed conditions.

Ombitasvir is predominantly metabolized by amide hydrolysis followed by oxidative metabolism. Paritaprevir is predominantly metabolized by CYP3A4 and, to a lesser extent, by CYP3A5. Ritonavir is predominantly metabolized by CYP3A and, to a lesser extent, by CYP2D6. Dasabuvir is predominantly metabolized by CYP2C8 and, to a lesser extent, by CYP3A. Ombitasvir/paritaprevir/ritonavir + dasabuvir are primarily eliminated in the feces.

Sofosbuvir

After oral administration, sofosbuvir (Sovaldi) is rapidly converted to the predominant circulating metabolite GS-331007, which lacks anti-HCV activity *in vitro.* GS-331007 accounts for greater than 90% of drug-related material systemic exposure, while the parent sofosbuvir accounts for approximately 4% of drug-related material. Following oral administration of sofosbuvir under fasting conditions, peak plasma concentrations were observed at 0.5 to 2 hours post-dose and this was not substantially altered when sofosbuvir was administered with a high fat meal. Sofosbuvir is extensively metabolized in the liver to form the pharmacologically active nucleoside analog triphosphate GS-461203. The terminal half-life of sofosbuvir is 0.4 hours and is 27 hours for GS-331007. Renal clearance is the predominant elimination pathway. Exposure of sofosbuvir and GS-331007 in pediatric patients ≥ 3 years of age is similar to that observed in adults.

Velpatasvir

Velpatasvir reaches its mean peak concentration approximately 3 hours after oral administration. The pharmacokinetics of velpatasvir is not significantly altered by meals and can be administered without regard to food. Velpatasvir is metabolized by cytochrome P450 isoenzymes CYP2B6, CYP2C8, and CYP3A4. Velpatasvir is eliminated primarily by biliary excretion unchanged. Exposure of velpatasvir in pediatric patients ≥ 3 years of age is similar to that observed in adults.

Voxilaprevir

Voxilaprevir reaches its mean peak concentration approximately 4 hours after oral administration. The pharmacokinetics of voxilaprevir is significantly altered by meals and should be administered with food. Voxilaprevir is highly protein bound and is primarily metabolized by CYP3A4 with secondary metabolism by CYP1A2 and CYP2C8. The majority of voxilaprevir, approximately 94%, is eliminated through biliary excretion.

CONTRAINDICATIONS/WARNINGS[70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86]

Contraindications and warnings for an agent also apply when that agent is used as part of a combination regimen.

Interferons

Contraindications

Peginterferon alfa-2a (Pegasys) is contraindicated in the presence of hypersensitivity to any of the product components, hepatic decompensation (Child-Pugh B and C) in cirrhotic CHC patients before treatment, and in the presence of hepatic decompensation in cirrhotic CHC patients coinfected with HIV before treatment.

Benzyl alcohol is associated with an increased incidence of neurologic and other complications in neonates and infants, which are sometimes fatal; therefore, peginterferon alfa-2a (Pegasys) is contraindicated in neonates and infants.

Peginterferon alfa-2a and ribavirin combination is contraindicated when given concurrently with didanosine due to reports of fatal hepatic failure and peripheral neuropathy, pancreatitis, and symptomatic hyperlactatemia/lactic acidosis.

Warnings

All of the alpha interferons indicated for HCV, including peginterferons, have the following boxed warning: alpha interferons cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Serious and severe infections due to bacterial, fungal, or viral pathogens have been reported with the alpha interferons, including some fatal infections. Patients should be monitored closely with periodic clinical and laboratory evaluations. Patients with persistently severe or worsening signs or symptoms of these conditions should be withdrawn from therapy. In many, but not all cases, these disorders resolved after stopping interferon therapy.

Life-threatening or fatal neuropsychiatric events including suicides, suicidal and homicidal ideation, depression, and relapse of drug addiction/overdose may manifest in patients receiving therapy with peginterferon alfa. Adverse neuropsychiatric events reported with alfa interferons include aggressive behavior, psychoses, hallucinations, bipolar disorder, and mania. These reactions may occur in patients with or without previous psychiatric illness. Patients on therapy should receive close monitoring for the occurrence of depressive symptomatology. Patients with persistently severe or worsening neuropsychiatric signs or symptoms should be withdrawn from therapy. These agents should be used with extreme caution in patients with a history of psychiatric illness. If interferon treatment is deemed necessary in patients with a prior history or existence of psychiatric disorder or with a history of substance use disorders, treatment requires individualized drug screening strategies and frequent psychiatric symptom monitoring. Early intervention for re-emergence or development of neuropsychiatric symptoms and substance abuse is recommended.

Peginterferon alfa suppresses bone marrow function and may result in severe cytopenias, including neutropenia and lymphopenia and very rare events of aplastic anemia. It is advised that complete blood counts be obtained pre-treatment and monitored routinely during therapy. Interferon alfa should be discontinued in patients who develop severe decreases in neutrophils ($< 0.5 \times 10^9$/L) or platelet counts ($< 25 \times 10^9$/L). Severe neutropenia and thrombocytopenia occur with a greater incidence in HIV coinfected patients than monoinfected patients and may result in serious infections or bleeding. Serious bacterial, fungal, and viral infections, some fatal, have been observed in interferon-treated patients. Some infections have been associated with severe neutropenia.

Peginterferon alfa should be used with caution in patients with cardiac disease. Chest pain, changes in blood pressure, supraventricular arrhythmias, and myocardial infarctions have occurred. Patients with a history of significant or unstable cardiac disease should not be treated with peginterferon and ribavirin therapy.

Peginterferon alfa also affects the endocrine system, either causing or aggravating hyperthyroidism or hypothyroidism, as well as hyperglycemia or hypoglycemia. New onset diabetes including type 1 diabetes mellitus has been reported. One study showed thyroid dysfunction occurring in 11.8% of 254 patients being treated for chronic hepatitis C with interferon alfa plus ribavirin combination therapy.[87]

Neither interferon alfa dosage nor the virologic response to treatment was related to the incidence of thyroid dysfunction, of which two-thirds was hypothyroidism and one-third was hyperthyroidism.

Pulmonary disorders, colitis (ulcerative and hemorrhagic/ischemic), and pancreatitis have occurred following use of peginterferon alfa. Decreases in or loss of vision, retinopathy, retinal vessel thrombosis, optic neuritis, serious retinal detachment, and papilledema are induced or aggravated by treatment with interferon alfa. Cerebral vascular events, both thrombotic and hemorrhagic, have been reported with patients receiving interferon alfa therapy; events occurred in patients with few or no other risk factors for stroke, including patients less than 45 years of age. Due to fever and flu-like symptoms from peginterferon, use caution when using peginterferon in patients with debilitating medical conditions, such as those with a history of pulmonary disease.

Patients with CHC with cirrhosis may be at risk of hepatic decompensation and death when treated with alpha interferons. Initiation of peginterferon alfa therapy has been reported to cause transient liver abnormalities, which can result in increased ascites, hepatic failure, or death in patients with poorly compensated liver disease. Therapy should be discontinued for any patient developing signs and symptoms of liver failure. There are very little data regarding use of peginterferon alfa in immunosuppressed patients or transplant recipients.

Patients with cirrhosis due to CHC and also infected with HIV who receive highly active antiretroviral therapy (HAART) and interferon alfa-2a, with or without ribavirin, appear to be at increased risk for the development of hepatic decompensation compared to patients not receiving HAART. Patients' clinical status and hepatic function should be closely monitored and peginterferon should be immediately discontinued in patients with hepatic decompensation.

Peginterferon alfa should be used with caution in patients with a history of autoimmune disease.

Ribavirin

Contraindications

Ribavirin is contraindicated in patients with hemoglobinopathies (e.g., thalassemia major, sickle cell anemia). Ribavirin is contraindicated in patients with known hypersensitivity to ribavirin or to any component of the product. Co-administration of ribavirin (generics for Rebetol) and didanosine is contraindicated because exposure to the active metabolite of didanosine (dideoxyadenosine 5'-triphosphate) is increased. Fatal hepatic failure, as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactatemia/lactic acidosis, have been reported in patients receiving both didanosine and ribavirin.

Ribavirin is contraindicated in females who are pregnant and in the male partners of females who are pregnant. Ribavirin is Pregnancy Category X. Ribavirin exposure may cause birth defects and/or death of the exposed fetus. Ribavirin therapy should not be started unless a negative pregnancy test has been obtained immediately prior to the initiation of ribavirin therapy. Female patients should use effective forms of contraception during therapy and for 9 months after treatment has stopped. Monthly pregnancy testing should be performed during and for 9 months after therapy has been discontinued. Male patients and their female partners should use effective forms of contraception during therapy and for 6 months after treatment has stopped. Ribavirin is genotoxic and mutagenic and should be considered a potential carcinogen.

Ribavirin is contraindicated in patients with autoimmune hepatitis, hepatic decompensation (Child-Pugh B or C) in cirrhotic patients with CHC before or during therapy, and hepatic decompensation in cirrhotic CHC patients coinfected with HIV before or during therapy.

Warnings

The primary toxicity of ribavirin is hemolytic anemia. Hemolytic anemia was observed in approximately 10% of patients treated with interferon alfa plus ribavirin in clinical trials and usually occurred within 1 to 2 weeks of initiation of ribavirin therapy. Cardiac and pulmonary events have occurred in approximately 10% of patients with hemolytic anemia. Patients with a history of significant or unstable cardiac disease should not be treated with ribavirin. Caution should be exercised in starting treatment in any patient with an increased risk of severe anemia (e.g., history of gastrointestinal bleeding).

Patients with estimated creatinine clearance (CrCl) < 50 mL/minute should not receive ribavirin.

Severe depression and suicidal or homicidal ideation have been reported in patients taking both ribavirin and interferon.

NS5B Polymerase Inhibitor – sofosbuvir (Sovaldi)

Contraindications

When used in combination with peginterferon and/or ribavirin, all contraindications to peginterferon and ribavirin also apply; see above information on interferons and ribavirin for details.

Warnings

All DAAs carry a boxed warning for the risk of HBV reactivation, in certain patients who have had a current or previous infection with HBV. In some patients, HBV reactivation resulted in serious liver problems or death. Therefore, all patients should be screened for HBV prior to starting DAAs and monitored for HBV flare-ups or reactivation while receiving DAA medications and post-treatment follow-up.[88,89]

Drugs that are potent P-gp inducers in the intestine (e.g., rifampin, St. John's wort) may significantly decrease sofosbuvir plasma concentrations and may lead to a reduced therapeutic effect of sofosbuvir (Sovaldi). Rifampin and St. John's wort should not be used with sofosbuvir.

Coadministration of sofosbuvir with anticonvulsants (carbamazepine, phenytoin, phenobarbital, or oxcarbazepine), antimycobacterial antibiotics (rifabutin, rifapentine, rifampin), and the HIV protease inhibitor combination tipranavir/ritonavir is not recommended since it can lead to a reduced therapeutic effect of sofosbuvir.

Coadministration of amiodarone with sofosbuvir in combination with another DAA is not recommended due to the risk of serious symptomatic bradycardia, particularly in patients also receiving beta-blockers or those with underlying cardiac comorbidities and/or advanced liver disease. In patients with no alternative treatment options, cardiac monitoring is recommended. A case of fatal cardiac arrest was reported in a patient taking amiodarone who was co-administered a sofosbuvir-containing regimen (ledipasvir/sofosbuvir).

Sofosbuvir should not be used with other products containing sofosbuvir.

Combination Products – elbasvir/grazoprevir (Zepatier)

Contraindications

Elbasvir/grazoprevir is contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh B or C) or those with any history of hepatic decompensation due to the risk of hepatic decompensation, and in patients who are taking concomitant OATP1B1/3 inhibitors that are known or expected to significantly increase grazoprevir plasma concentrations, strong CYP3A inducers, or efavirenz.

The following medications are contraindicated with elbasvir/grazoprevir due to drug interactions: anticonvulsants (e.g., phenytoin, carbamazepine), antimycobacterials (e.g., rifampin), herbal products (e.g., St. John's wort), HIV medications (e.g., efavirenz, atazanavir, darunavir, lopinavir, saquinavir, tipranavir), and immunosuppressants (e.g., cyclosporine).

Warnings

All DAAs carry a boxed warning for HBV reactivation, as described above.[90,91]

During clinical trials with elbasvir/grazoprevir with or without ribavirin, 1% of subjects experienced elevations of ALT from normal levels to greater than 5 times the upper limit of normal (ULN). Hepatic laboratory testing should be performed prior to therapy, at treatment week 8, and as clinically indicated. For patients receiving 16 weeks of therapy, additional hepatic laboratory testing needs to be performed at treatment week 12. For ALT elevations on elbasvir/grazoprevir, discontinuation of the drug should be considered if the elevation is greater than 10 times the ULN or if the ALT elevation is accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or international normalized ratio (INR).

Concomitant use of elbasvir/grazoprevir with certain drugs may result in significant interactions.

In August 2019, in the FDA issued a safety announcement regarding cases of worsening liver function or liver failure with 3 combination products: glecaprevir/pibrentasvir (Mavyret), elbasvir/grazoprevir (Zepatier), and sofosbuvir/velpatasvir/voxilaprevir (Vosevi).[92] This is thought to be related to the protease inhibitor component. In many cases, liver failure occurred in patients who had signs or symptoms of moderate to severe liver impairment prior to treatment. As a result, the product labeling for these agents was updated. Elbasvir/grazoprevir is not recommended in patients with moderate to severe hepatic impairment (Child-Pugh B or C) or in patients with a history of hepatic decompensation and should be discontinued in patients who develop evidence or hepatic decompensation or failure.

Combination Products – glecaprevir/pibrentasvir (Mavyret)

Contraindications

Glecaprevir/pibrentasvir (Mavyret) is contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh C) and in patients with any history of prior hepatic impairment.

Glecaprevir/pibrentasvir (Mavyret) is contraindicated in patients taking atazanavir due to an increased risk of ALT elevations.

Glecaprevir/pibrentasvir (Mavyret) is contraindicated in patients taking rifampin due to a decrease in concentration of both components which could result in loss of efficacy.

Warnings

All DAAs carry a boxed warning for HBV reactivation, as described above.[93,94]

Glecaprevir/pibrentasvir carries a warning regarding the risk of reduced efficacy when used concomitantly with carbamazepine, efavirenz, or St. John's wort. Concurrent use is not recommended.

As described above, postmarketing cases of hepatic decompensation and hepatic failure in patients being treated for hepatitis C using NS3/4A protease inhibitor containing regimens, including glecaprevir/pibrentasvir, have been reported. This combination is not recommended in patients with moderate to severe hepatic impairment (Child-Pugh B or C) or in patients with a history of hepatic decompensation and should be discontinued in patients who develop evidence or hepatic decompensation or failure.

Combination Products – ledipasvir/sofosbuvir (Harvoni)

Contraindications

There are no contraindications to treatment with ledipasvir/sofosbuvir.

Warnings

All DAAs carry a boxed warning for HBV reactivation, as described above.[95,96]

The concomitant use of ledipasvir/sofosbuvir and P-gp inducers (e.g., rifampin, St. John's wort) may significantly decrease the plasma concentrations of both ledipasvir and sofosbuvir and, therefore, may lead to a reduced therapeutic effect. The combination of ledipasvir/sofosbuvir with P-gp inducers is not recommended. Ledipasvir/sofosbuvir should not be used in combination with other products containing sofosbuvir.

Co-administration of amiodarone with ledipasvir/sofosbuvir is not recommended due to the risk of serious symptomatic bradycardia, particularly in patients also receiving beta-blockers or those with underlying cardiac comorbidities and/or advanced liver disease. In patients with no alternative treatment options, cardiac monitoring is recommended. A case of fatal cardiac arrest was reported in a patient taking amiodarone who was co-administered a sofosbuvir-containing regimen (ledipasvir/sofosbuvir).

Co-administration of ledipasvir/sofosbuvir with anticonvulsants (carbamazepine, phenytoin, phenobarbital, or oxcarbazepine), antimycobacterial antibiotics (rifabutin, rifapentine, rifampin), and the HIV protease inhibitor combination tipranavir/ritonavir is not recommended since it can lead to a reduced therapeutic effect of ledipasvir/sofosbuvir.

Combination Products – ombitasvir/paritaprevir/ritonavir and dasabuvir (Viekira Pak)

Contraindications

Ombitasvir/paritaprevir/ritonavir + dasabuvir (Viekira Pak) is contraindicated in patients with moderate and severe hepatic impairment (Child-Pugh B and C).

Ombitasvir/paritaprevir/ritonavir + dasabuvir (Viekira Pak) is contraindicated for use with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events.

Ombitasvir/paritaprevir/ritonavir + dasabuvir (Viekira Pak) is contraindicated with drugs that are moderate or strong inducers of CYP3A and strong inducers of CYP2C8 due to the possible reduced efficacy of Viekira Pak.

Ombitasvir/paritaprevir/ritonavir + dasabuvir (Viekira Pak) is contraindicated for use with drugs that are strong inhibitors of CYP2C8 due to the possible increase in dasabuvir plasma concentrations and the risk of QT prolongation.

Ombitasvir/paritaprevir/ritonavir + dasabuvir (Viekira Pak) is contraindicated in patients with known hypersensitivity (e.g., toxic epidermal necrolysis [TEN] or Stevens-Johnson syndrome) to ritonavir.

Ombitasvir/paritaprevir/ritonavir + dasabuvir (Viekira Pak) is contraindicated with the following drugs: alfuzosin, ranolazine, dronedarone, carbamazepine, colchicine, phenytoin, phenobarbital, apalutamide, gemfibrozil, rifampin, lurasidone, pimozide, ergotamine, dihydroergotamine, ergonovine, methylergonovine, ethinyl estradiol-containing medications, such as combined oral contraceptives, cisapride, St. John's wort, atorvastatin, lovastatin, simvastatin, everolimus, sirolimus, tacrolimus, lomitapide, efavirenz, sildenafil (when dosed for the treatment of pulmonary arterial hypertension), triazolam, and orally-administered midazolam.

Warnings

All DAAs carry a boxed warning for HBV reactivation, as described above.[97,98]

Hepatic decompensation and failure, including cases requiring liver transplantation or resulting in a fatal outcome, have been reported with ombitasvir/paritaprevir/ritonavir + dasabuvir (Viekira Pak) use. Acute onset of elevated direct serum bilirubin without ALT elevations characterized most cases, and most occurred within 1 to 4 weeks of treatment onset. For patients with cirrhosis, baseline and every 4-week hepatic laboratory testing should be performed as clinically indicated, and Viekira Pak should be discontinued in patients who develop hepatic decompensation. Monitoring for signs and symptoms of hepatic decompensation is also recommended.

There is an increased risk of ALT elevations in patients taking ombitasvir/paritaprevir/ritonavir + dasabuvir (Viekira Pak) with or without ribavirin. Elevations of ALT to greater than 5 times the upper limit of normal (ULN) occurred in approximately 1% of all subjects during clinical trials. ALT elevations typically occurred during the first 4 weeks of treatment and declined within 2 to 8 weeks of onset with continued dosing of Viekira Pak with or without ribavirin. These ALT elevations were significantly more common in female subjects who were using ethinyl estradiol-containing oral contraceptives, contraceptive patches, or contraceptive vaginal rings. Liver function tests should be performed during the first 4 weeks of starting treatment and as clinically indicated thereafter. Consideration should be given to discontinuing ombitasvir/paritaprevir/ritonavir + dasabuvir (Viekira Pak) if ALT levels remain persistently greater than 10 times the ULN. Ombitasvir/paritaprevir/ritonavir + dasabuvir (Viekira Pak) should be discontinued if ALT elevation is accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or INR.

Treatment of HCV/HIV-1 coinfected patients with ombitasvir/paritaprevir/ritonavir + dasabuvir (Viekira Pak) can select for HIV-1 protease inhibitor resistance-associated substitutions. Any HCV/HIV-1 coinfected patients utilizing ombitasvir/paritaprevir/ritonavir + dasabuvir (Viekira Pak) should also be on a suppressive antiretroviral drug regimen to reduce the risk of HIV-1 protease inhibitor drug resistance.

Combination Products – sofosbuvir/velpatasvir (Epclusa)

Contraindications

When used in combination with ribavirin, all contraindications to ribavirin also apply; see above information on interferons and ribavirin for details.

Warnings

All DAAs carry a boxed warning for HBV reactivation, as described above.[99,100]

Serious symptomatic bradycardia may occur in patients taking amiodarone, particularly in patients also receiving beta-blockers or those with underlying cardiac comorbidities and/or advanced liver disease. Co-administration of amiodarone with sofosbuvir/velpatasvir is not recommended. In patients without alternative viable treatment options, cardiac monitoring, including initial monitoring in an inpatient setting, is recommended.

Sofosbuvir/velpatasvir also carries a warning regarding reduced efficacy when used concomitantly with P-glycoprotein (P-gp) inducers and/or moderate to potent inducers of cytochrome P450, specifically CYP2B6, CYP2C8, and CYP3A4. Concurrent use is not recommended.

Co-administration of sofosbuvir/velpatasvir with anticonvulsants (carbamazepine, phenytoin, phenobarbital, or oxcarbazepine), antimycobacterial antibiotics (rifabutin, rifapentine, or rifampin), the HIV protease inhibitor combination tipranavir/ritonavir, efavirenz, or topotecan is not recommended since it can lead to reduced therapeutic effect of sofosbuvir/velpatasvir.

Combination Products – sofosbuvir/velpatasvir/voxilaprevir (Vosevi)

Contraindications

Sofosbuvir/velpatasvir/voxilaprevir is contraindicated in patients taking rifampin due to a decrease in concentration of voxilaprevir which could result in loss of efficacy.

Warnings

All DAAs carry a boxed warning for HBV reactivation, as described above.[101,102]

Serious symptomatic bradycardia may occur in patients taking amiodarone, particularly in patients also receiving beta-blockers or those with underlying cardiac comorbidities and/or advanced liver disease. Co-administration of amiodarone with sofosbuvir/velpatasvir/voxilaprevir is not recommended. In patients without alternative viable treatment options, cardiac monitoring, including initial monitoring in an inpatient setting, is recommended.

Sofosbuvir/velpatasvir/voxilaprevir carries a warning regarding the risk of reduced efficacy when used concomitantly with P-gp inducers and/or moderate to potent inducers of cytochrome P450, specifically CYP2B6, CYP2C8, and CYP3A4. Concurrent use is not recommended.

Co-administration of sofosbuvir/velpatasvir with anticonvulsants (carbamazepine, phenytoin, phenobarbital, or oxcarbazepine); antimycobacterial antibiotics (rifabutin, rifapentine, rifampin); antiretrovirals (atazanavir, efavirenz, lopinavir, and tipranavir/ritonavir); HMG-CoA reductase inhibitors (rosuvastatin, pitavastatin); topotecan; or cyclosporine is not recommended since it can lead to a reduced therapeutic effect of sofosbuvir/velpatasvir.

As described above, postmarketing cases of hepatic decompensation and hepatic failure in patients being treated for hepatitis C using NS3/4A protease inhibitor containing regimens, including glecaprevir/pibrentasvir, have been reported. This combination is not recommended in patients with moderate to severe hepatic impairment (Child-Pugh B or C) or in patients with a history of hepatic decompensation and should be discontinued in patients who develop evidence of hepatic decompensation or failure.

Risk Evaluation and Mitigation Strategy (REMS)

None of the agents within this class require REMS.

DRUG INTERACTIONS[103,104,105,106,107,108,109,110,111,112,113,114,115,116,117]

Concomitant treatment with warfarin and HCV treatment including elbasvir/grazoprevir (Zepatier), glecaprevir/pibrentasvir (Mavyret), ledipasvir/sofosbuvir (Harvoni), ombitasvir/paritaprevir/ritonavir + dasabuvir (Viekira Pak), sofosbuvir (Sovaldi), sofosbuvir/velpatasvir (Epclusa), and sofosbuvir/velpatasvir/ voxilaprevir (Vosevi) may cause fluctuations in INR values. Frequent monitoring of INR values during treatment and post-treatment is recommended.

The treatment of hepatitis C with direct acting antivirals including ledipasvir/sofosbuvir (Harvoni), sofosbuvir (Sovaldi), sofosbuvir/velpatasvir (Epclusa), and sofosbuvir/velpatasvir/voxilaprevir (Vosevi) may lead to changes in hepatic function may impact the safe and effective use of concomitant medications; for example, changes in blood glucose control may result. Postmarketing reports of serious symptomatic hypoglycemia in diabetic patients have been reported requiring modification or discontinuation of the medications used for the treatment of diabetes.

Interferon

Concomitant use of peginterferon alfa and theophylline may result in a significant increase in theophylline concentrations. Consider monitoring theophylline levels and adjusting theophylline therapy accordingly during peginterferon therapy. Peginterferon alfa has also been reported to inhibit activity of CYP 450 enzymes, although this interaction is thought to be of minimal clinical significance.

Peginterferons have synergistic toxicities when given with myelosuppressive agents, such as antineoplastics and zidovudine.

Ribavirin

Ribavirin may reduce phosphorylation of lamivudine, stavudine, and zidovudine based on *in vitro* studies. No pharmacokinetic or pharmacodynamic interactions were observed in small studies when ribavirin and lamivudine, stavudine, or zidovudine was co-administered as a part of a multiple drug regimen for the treatment of HCV/HIV coinfected patients. Ribavirin and didanosine co-administration may result in increased exposure to didanosine and its metabolites; closely monitor for toxicities and consider discontinuation with worsening toxicities.

Ribavirin co-administered with azathioprine has resulted in pancytopenia with marked decreases in red blood cells, neutrophils, and platelets. Bone marrow suppression has been reported to occur within 3 to 7 weeks after the concomitant administration of peginterferon and ribavirin with azathioprine. In the 8

reported cases, myelosuppression was reversible over 4 to 6 weeks upon withdrawal of all 3 agents and did not recur upon reintroduction of either treatment alone.

A retrospective cohort study evaluating the effect of HCV medications on warfarin levels found that ribavirin has an impact on warfarin sensitivity. Thus, the authors recommend increased laboratory monitoring in patients who are using concomitant warfarin to ensure appropriate anticoagulation.[118]

Elbasvir/grazoprevir

Grazoprevir is a substrate of OATP1B1/3 transporters. Co-administration of elbasvir/grazoprevir with drugs that inhibit OATP1B1/3 transporters may result in a significant increase in the plasma concentrations of grazoprevir. As such, co-administration of elbasvir/grazoprevir with OATP1B1/3 inhibitors is contraindicated as discussed above. Elbasvir and grazoprevir are substrates of CYP3A and P-gp, but the role of intestinal P-gp in the absorption of elbasvir and grazoprevir appears to be minimal. Co-administration of moderate or strong inducers of CYP3A with elbasvir/grazoprevir may decrease elbasvir and grazoprevir plasma concentrations, leading to reduced therapeutic effect of elbasvir/grazoprevir. Co-administration of elbasvir/grazoprevir with strong CYP3A inducers or efavirenz is contraindicated. Co-administration of elbasvir/grazoprevir with moderate CYP3A inducers is not recommended. Co-administration of elbasvir/grazoprevir with strong CYP3A inhibitors may increase elbasvir and grazoprevir concentrations. Co-administration of elbasvir/grazoprevir with certain strong CYP3A inhibitors is not recommended.

Concomitant administration with the following agents may decrease the efficacy of elbasvir/grazoprevir: nafcillin, bosentan, modafinil, and etravirine. Concomitant administration with the following agents may increase exposure to elbasvir/grazoprevir: ketoconazole and elvitegravir/cobicistat/emtricitabine/tenofovir (disoproxil fumarate or alafenamide). Use of elbasvir/grazoprevir may increase the exposure of the following agents when used concomitantly: tacrolimus and HMG-CoA reductase inhibitors (e.g., atorvastatin, rosuvastatin, fluvastatin, lovastatin, simvastatin).

Glecaprevir/pibrentasvir

Glecaprevir and pibrentasvir are substrates of P-gp and/or BCRP. Glecaprevir is a substrate of OATP1B1/3. Co-administration of glecaprevir/pibrentasvir therapy with the following inducers of P-gp and/or CYP3A may decrease the concentration of glecaprevir/pibrentasvir: carbamazepine, efavirenz, phenytoin, rifampin, and St. John's wort. Co-administration is not recommended. All drug interaction studies were performed in adult patients.

Ledipasvir

Ledipasvir solubility decreases as pH increases. Drugs that increase gastric pH are expected to decrease the concentration of ledipasvir. Antacids, H_2-receptor antagonists (e.g., famotidine), and proton pump inhibitors (e.g., omeprazole) may all decrease ledipasvir concentrations.

Carbamazepine, oxcarbazepine, phenytoin, and phenobarbital are expected to decrease the concentration of ledipasvir and sofosbuvir and co-administration with these agents is not recommended.

Co-administration of ledipasvir/sofosbuvir with digoxin may increase the concentration of digoxin and therapeutic drug monitoring of digoxin is recommended.

Rifampin and other rifamycin derivatives, including rifabutin and rifapentine, may decrease ledipasvir and sofosbuvir concentrations and co-administration with these agents is not recommended.

Tenofovir concentrations are increased and tenofovir-associated adverse reactions may occur in patients receiving ledipasvir/sofosbuvir in combination with antiretroviral regimens that include tenofovir. No clinically significant drug interactions have been observed when ledipasvir/sofosbuvir is administered with the following antiretroviral agents when they are administered individually and not as part of an HIV-combination regimen: abacavir, atazanavir/ritonavir, darunavir/ritonavir, efavirenz, emtricitabine, lamivudine, raltegravir, rilpivirine, and tenofovir disoproxil fumarate. The concentration of ledipasvir is increased when they are co-administered and this combination is not recommended.

St. John's wort decreases both ledipasvir and sofosbuvir concentrations and co-administration is not recommended. Co-administration of ledipasvir/sofosbuvir with HMG-CoA reductase inhibitors, including rosuvastatin and atorvastatin, may significantly increase the concentration of the HMG-CoA reductase inhibitor leading to an increased risk of myopathy, including rhabdomyolysis. Co-administration with rosuvastatin is not recommended. A patient taking atorvastatin concomitantly, should be monitored for adverse reactions, including myopathy and rhabdomyolysis.

Ombitasvir/paritaprevir/ritonavir with and without dasabuvir

Co-administration of ombitasvir/paritaprevir/ritonavir + dasabuvir (Viekira Pak) with strong inhibitors of CYP3A may increase paritaprevir and ritonavir concentrations. Co-administration of Viekira Pak with drugs that inhibit CYP2C8 may increase dasabuvir plasma concentrations. Inhibition of P-gp, BCRP, OATP1B1, or OATP1B3 may increase the plasma concentrations of the various components of Viekira Pak.

Co-administration of Viekira Pak with drugs that are substrates of CYP3A, UGT1A1, BCRP, OATP1B1, or OATP1B3 may result in increased plasma concentrations of such drugs due to inhibition by the various components of Viekira Pak.

Concomitant therapy with ombitasvir/paritaprevir/ritonavir + dasabuvir (Viekira Pak) could increase concentrations of the following interacting medications: antiarrhythmics (amiodarone, bepridil, disopyramide, flecainide, lidocaine [systemic], mexiletine, propafenone, quinidine), antifungals (ketoconazole), calcium channel blockers (amlodipine, nifedipine, diltiazem, verapamil), colchicine, corticosteroids (fluticasone), diuretics (furosemide), HMG CoA reductase inhibitors (rosuvastatin, pravastatin), immunosuppressants (cyclosporine, tacrolimus), narcotic analgesics (buprenorphine, fentanyl, hydrocodone), antipsychotics (quetiapine), sedatives/hypnotics (alprazolam), and angiotensin receptor blockers (valsartan, losartan, candesartan).

Concomitant therapy with ombitasvir/paritaprevir/ritonavir + dasabuvir (Viekira Pak) could decrease the concentration of darunavir and omeprazole.

Concomitant therapy with ombitasvir/paritaprevir/ritonavir + dasabuvir (Viekira Pak) has been shown to interact with the following medications and co-administration is not recommended: certain antifungals (voriconazole), certain HIV antivirals (darunavir/ritonavir, lopinavir/ritonavir, rilpivirine), and certain long-acting beta-agonists (salmeterol).

A retrospective cohort study evaluating the effect of sofosbuvir-containing medications or ombitasvir/paritaprevir/ritonavir + dasabuvir on warfarin levels found that the combination increased

warfarin sensitivity. Thus, the authors recommend increased laboratory monitoring in patients who are using concomitant warfarin to ensure appropriate anticoagulation.[119]

Sofosbuvir

Sofosbuvir (Sovaldi) is a substrate of drug transporter P-gp and breast cancer resistance protein (BCRP). Drugs that are potent P-gp inducers in the intestine (e.g., rifampin or St. John's wort) may decrease sofosbuvir plasma concentration leading to reduced therapeutic effect of sofosbuvir and thus should not be used with sofosbuvir.

In addition, administration of sofosbuvir with carbamazepine, phenytoin, phenobarbital, rifabutin, rifapentine, or tipranavir/ritonavir is expected to decrease the concentration of sofosbuvir and co-administration is not recommended.

Co-administration of sofosbuvir (Sovaldi) and other oral direct acting antivirals, including the combination product ledipasvir/sofosbuvir (Harvoni), with amiodarone may result in serious symptomatic bradycardia, particularly in patients also receiving beta-blockers or those with underlying cardiac comorbidities and/or advanced liver disease. In patients with no alternative treatment options, cardiac monitoring is recommended.

A retrospective cohort study evaluating the effect of HCV medications on warfarin levels found that sofosbuvir (alone and with ledipasvir) has an impact on warfarin sensitivity. Thus, the authors recommend increased laboratory monitoring in patients who are using concomitant warfarin to ensure appropriate anticoagulation.[120]

Sofosbuvir/velpatasvir

Sofosbuvir and velpatasvir are substrates of P-gp and breast cancer resistance protein (BCRP). Concomitant sofosbuvir/velpatasvir therapy with the following inducers of P-gp and/or moderate to potent inducers of CYP2B6, CYP2C8, or CYP3A4 may decrease the concentration of sofosbuvir/velpatasvir: efavirenz, phenytoin, phenobarbital, carbamazepine, oxcarbazepine, rifampin, rifabutin, rifapentine, St. John's wort, and tipranavir/ritonavir. Co-administration is not recommended.

Concomitant therapy with the following medications could decrease the concentration of sofosbuvir/velpatasvir due to decreased gastric pH: antacids (aluminum and magnesium hydroxide), H2-receptor antagonists, and proton-pump inhibitors (PPIs). Separate administration time of antacids by 4 hours. H2-receptor antagonists may be given simultaneously with sofosbuvir/velpatasvir or 12 hours apart at doses ≤ 40 mg twice daily of famotidine or the equivalent. If co-administration with a PPI is unavoidable (e.g., medically necessary), administer sofosbuvir/velpatasvir with food 4 hours prior to administration of omeprazole 20 mg; use with other PPIs has not been studied.

Concomitant therapy with amiodarone is not recommended due to the risk of serious symptomatic bradycardia as described above.

Velpatasvir is an inhibitor of drug transporters P-gp, BCRP, OATP1B1, OATP1B3, and OATP2B1. Concomitant therapy with sofosbuvir/velpatasvir could increase concentrations of the following interacting medications: digoxin, topotecan, tenofovir, HMG CoA reductase inhibitors (e.g., atorvastatin, rosuvastatin). Additional monitoring and/or dose adjustments of the concomitant agent may be required; co-administration with topotecan is not recommended.

Sofosbuvir/velpatasvir/voxilaprevir

Sofosbuvir, velpatasvir, and voxilaprevir are substrates of P-gp and BCRP. Voxilaprevir is also a substrate of OATP1B1 and OATP1B3. Concomitant sofosbuvir/velpatasvir/voxilaprevir therapy with the following inducers of P-gp and/or moderate to potent inducers of CYP2B6, CYP2C8, or CYP3A4 may decrease the concentration of sofosbuvir/velpatasvir/voxilaprevir: efavirenz, phenytoin, phenobarbital, carbamazepine, oxcarbazepine, rifampin, rifabutin, rifapentine, St. John's wort, and tipranavir/ritonavir. Co-administration is not recommended. Concomitant use with OATP inhibitors that may substantially increase the exposure of voxilaprevir (e.g., cyclosporine) is not recommended.

Velpatasvir and voxilaprevir are inhibitors of drug transporters P-gp, BCRP, OATP1B1, and OATP1B3. Velpatasvir is also an inhibitor of OATP2B1. Co-administration of sofosbuvir/velpatasvir/voxilaprevir with substrates of these transporters may alter the exposure of such drugs.

ADVERSE EFFECTS[121,122,123,124,125,126,127,128,129,130,131,132,133,134,135]

Drug	Depression	Fever	Injection Site Reaction	Anemia	Neutropenia	Withdrawal Rate
Monotherapy						
peginterferon alfa-2a (Pegasys) n=559	18	37	22	2	21	11
Dual Combination Therapy						
peginterferon alfa-2a (Pegasys) + ribavirin n=451	20	41	23	11	27	11
peginterferon alfa-2a (Pegasys) + ribavirin n=55	nr	nr	44	nr	nr	13
ribavirin + sofosbuvir (Sovaldi) for 24 weeks* n=250	nr	4	N/A	6	< 1	< 1
Triple Combination Therapy						
sofosbuvir (Sovaldi) plus peginterferon alfa/ribavirin for 12 weeks n=327	18	nr	59	21	17	2
peginterferon alfa/ribavirin for 24 weeks n=243	18	nr	55	12	12	11

nr = not reported
N/A = not applicable
* The adverse reactions observed in pediatric patients ≥ 12 years of age were consistent with those observed in clinical studies with this combination in adults.

Adverse Effects (continued)

Drug	Fatigue	Headache	Nausea	Diarrhea	Insomnia	Pruritus	Asthenia	Withdrawal Rate
All Oral Combination Therapy								
elbasvir/grazoprevir (Zepatier) for 12 weeks n=316	11	10	nr	nr	nr	nr	nr	nr
placebo for 12 weeks n=105	10	9	nr	nr	nr	nr	nr	nr
elbasvir/grazoprevir (Zepatier) for 12 weeks n=105	5	0	nr	2	nr	0	nr	nr
elbasvir/grazoprevir (Zepatier) + ribavirin for 16 weeks n=106	4	6	nr	0	nr	4	nr	nr
glecaprevir + pibrentasvir (Mavyret) for 8 weeks* n=157	11	16	9	7	nr	nr	nr	< 1
glecaprevir + pibrentasvir (Mavyret) for 12 weeks* n=233	14	17	12	3	nr	nr	nr	1
ledipasvir/sofosbuvir (Harvoni) for 8 weeks n=215	16	11	6	4	3	nr	nr	0
ledipasvir/sofosbuvir (Harvoni) for 12 weeks* n=539	13	14	7	3	5	nr	nr	< 1
ledipasvir/sofosbuvir (Harvoni) for 24 weeks n=326	18	17	9	7	6	nr	nr	1
ombitasvir/paritaprevir/ritonavir + dasabuvir (Viekira Pak) + ribavirin for 12 weeks n=770	34	nr	22	nr	14	18	14	< 1
placebo for 12 weeks n=255	26	nr	15	nr	8	7	7	nr

nr = not reported

*The adverse reactions observed in pediatric patients ≥ 12 years of age were consistent with those observed in clinical studies with this combination in adults.

Adverse Effects (continued)

Drug	Fatigue	Headache	Nausea	Diarrhea	Insomnia	Pruritus	Asthenia	Withdrawal Rate
All Oral Combination Therapy *(continued)*								
ombitasvir/paritaprevir/ ritonavir + dasabuvir (Viekira Pak) + ribavirin for 12 weeks in patients without cirrhosis n=401	nr	nr	16	nr	12	13	9	< 1
ombitasvir/paritaprevir/ ritonavir + dasabuvir (Viekira Pak) for 12 weeks in patients without cirrhosis n=509	nr	nr	8	nr	5	7	4	< 1
sofosbuvir + velpatasvir (Epclusa) for 12 weeks n=1,035	15	22	9	nr	5	nr	5	< 1
sofosbuvir + velpatasvir (Epclusa) for 12 weeks in patients with decompensated cirrhosis n=87	32	11	15	10	11	nr	nr	5
sofosbuvir + velpatasvir + voxilaprevir (Vosevi) for 12 weeks n=263	17	21	13	13	6	nr	6	< 1
sofosbuvir + velpatasvir + voxilaprevir (Vosevi) for 12 weeks n=182	19	23	10	14	3	nr	4	< 1

nr = not reported

N/A = not applicable

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all-inclusive.

*The adverse reactions observed in pediatric patients ≥ 12 years of age were consistent with those observed in clinical studies with this combination in adults.

The most common adverse events (≥ 20%) for sofosbuvir (Sovaldi) plus ribavirin combination therapy were fatigue and headache. The most common adverse events (≥ 20%) for sofosbuvir plus peginterferon alfa plus ribavirin combination therapy were fatigue, headache, nausea, insomnia, and anemia.

Nearly all patients receiving peginterferon alfa plus ribavirin will experience at least 1 adverse effect as a result of peginterferon alfa (such as neutropenia, thrombocytopenia, depression, thyroid disorders, irritability) and/or ribavirin (such as hemolytic anemia, fatigue, itching, rash, sinusitis). Adverse events tend to be more severe in the initial stages of treatment and can often be managed with analgesics, NSAIDs, and antidepressants. Growth factors, such as erythropoietin and filgrastim (Neupogen®), are sometimes used to counteract the adverse effects of ribavirin and peginterferon alfa.

Treatment adherence enhances SVR in patients with genotype 1 HCV.[136] Therefore, management of adverse effects to maintain patients on at least 80% of interferon or peginterferon alfa and ribavirin dosages for at least 80% of the duration of therapy will likely increase the chance for SVR.

Laboratory abnormalities occurring in less than 5% of patients taking ledipasvir/sofosbuvir (Harvoni) included bilirubin elevations of greater than 1.5 times the upper limit of normal (ULN) and transient, asymptomatic lipase elevations of greater than 3 times the ULN.

The most common adverse events occurring in at least 10% of patients treated with ombitasvir/paritaprevir/ritonavir + dasabuvir (Viekira Pak) and ribavirin who were coinfected with HCV/HIV included fatigue (48%), insomnia (19%), nausea (17%), headache (16%), pruritus (13%), cough (11%), irritability (10%), and ocular icterus (10%). Median declines in CD4+ T-cells of 47 cells/mm^3 and 62 cells/mm^3 were observed at the end of 12 and 24 weeks of treatment, respectively. No subject experienced an AIDS-related opportunistic infection.

Adverse events occurring in more than 20% of the 34 post-liver transplant subjects treated with Viekira Pak and ribavirin were fatigue (50%), headache (44%), cough (32%), diarrhea (26%), insomnia (26%), asthenia (24%), nausea (24%), muscle spasms (21%), and rash (21%). Ten of the 34 subjects underwent a ribavirin dose modification due to a decrease in hemoglobin and 1 patient required an interruption of ribavirin.

Post-baseline elevations in bilirubin at least 2 times ULN were observed in 15% of patients across all phase 3 studies receiving Viekira Pak with ribavirin compared to 2% of patients receiving Viekira Pak alone. These increases were predominantly indirect bilirubin and were attributed to the inhibition of bilirubin transporters OATP1B1/1B3 by paritaprevir, as well as ribavirin-induced hemolysis. In the study involving patients coinfected with HCV/HIV, 54% of subjects experienced total bilirubin elevations greater than 2 times ULN. Approximately half of the HCV/HIV coinfected patients who developed a bilirubin elevation greater than 2 times ULN were also receiving atazanavir.

Across all phase 3 studies, the mean change in hemoglobin levels from baseline was -2.4 g/dL in patients treated with Viekira Pak plus ribavirin compared to -0.5 g/dL in patients treated with Viekira Pak alone. Seven percent of patients treated with Viekira Pak plus ribavirin required a ribavirin dose reduction secondary to a decrease in hemoglobin levels, 3 subjects received a blood transfusion, and 5 patients were treated with erythropoietin. Only 1 patient discontinued therapy due to anemia. In the subset of HCV/HIV coinfected patients, 11% of patients had at least 1 post-baseline hemoglobin value of less than 10 g/dL and, in the post-liver transplant cohort, 29% of patients had at least 1 post-baseline hemoglobin value of less than 10 g/dL.

Hypersensitivity reactions have been reported with Viekira Pak.

Postmarketing reports of erythema multiforme and anaphylactic reactions have also been associated with Viekira Pak.

Serious skin reactions, such as rashes and/or angioedema, have been reported with sofosbuvir (Sovaldi), ledipasvir/sofosbuvir (Harvoni), and sofosbuvir/velpatasvir (Epclusa).

Additional adverse reactions reported with elbasvir/grazoprevir (Zepatier) include irritability (1%), depression (1%), and abdominal pain (2%). Elevations in serum ALT (5 times ULN, 1%) and bilirubin (2.5 times ULN, 6%) have been reported with elbasvir/grazoprevir. Decreased hemoglobin during treatment

has also been reported (mean for 12 weeks treatment, -0.3 g/dL; mean for 16 weeks treatment, -2.2 g/dL); however, hemoglobin normalized following discontinuation. Postmarketing reports of angioedema have also been associated with the use of elbasvir/grazoprevir. In an open-label trial of patients ≥ 12 years of age, adverse effects in pediatric patients were comparable to those observed in adults, with the most common adverse reactions of headache (14%) and nausea (9%).

In clinical trials, asymptomatic lipase elevations > 3 times ULN (2% to 6%) and creatine kinase ≥ 10 times ULN (1% to 2%) occurred more commonly in patients treated with sofosbuvir/velpatasvir (Epclusa) compared to patients treated with placebo (1% and 0%, respectively). Asymptomatic lipase elevations of > 3 times ULN occurred in 2% of patients taking sofosbuvir/velpatasvir/voxilaprevir (Vosevi) in clinical trials. Asymptomatic creatine kinase elevations ≥ 10 times ULN were reported in 1% of patients taking sofosbuvir/velpatasvir/ voxilaprevir in clinical trials.

An increase in total bilirubin of ≥ 2 times ULN occurred in 3.5% of subjects treated with glecaprevir/pibrentasvir versus 0% in placebo. No subjects experienced jaundice and total bilirubin levels decreased after completing therapy.

The adverse reactions observed in clinical trials with transplant patients who received sofosbuvir/velpatasvir (Epclusa) were consistent with the known safety profile of the combination. Adverse reactions were also similar between patients with and without compensated cirrhosis. The adverse reactions observed in an open-label phase 2 clinical trial with 103 adult patients with chronic HCV (genotype 1,2, 3,4) who inject drugs, including those on medication-assisted treatment for opioid use disorder were consistent with the known safety profile of the combination.

SPECIAL POPULATIONS[137,138,139,140,141,142,143,144,145,146,147,148,149,150,151]

Pediatrics

In August 2011, peginterferon alfa-2a (Pegasys) plus ribavirin was approved by the FDA for the treatment of chronic hepatitis C in previously untreated pediatric patients 5 to 17 years of age. Pediatric patients treated with peginterferon alfa-2a and ribavirin show a delay in weight and height increases after 48 weeks of therapy compared with their baseline. Long-term follow-up data in pediatric subjects is too limited to determine overall risk of reduced adult height.

Benzyl alcohol is associated with an increased incidence of neurologic and other complications in neonates and infants, which are sometimes fatal; therefore, peginterferon alfa-2a is contraindicated in neonates and infants.

Suicidal ideation or attempts occurred more frequently among pediatric patients, primarily adolescents, compared to adult patients (2.4% versus 1%) during treatment with ribavirin and off-therapy follow-up.

The safety, pharmacokinetics, and efficacy of sofosbuvir (Sovaldi) in pediatric patients ≥ 3 years of age with genotype 2 and 3 infection without cirrhosis or with compensated cirrhosis have been established (in combination with ribavirin).[152,153] The safety and efficacy of sofosbuvir have not been established in pediatric patients with genotypes 1 or 4 or in pediatric patients with genotype 2 or 3 who are < 3 years of age.

Safety and efficacy of glecaprevir/pibrentasvir (Mavyret) have not been established in pediatric patients < 3 years of age. The safety, pharmacokinetics, and efficacy of glecaprevir/pibrentasvir in pediatric

patients ≥ 3 years of age with genotype 1, 2, 3, 4, 5, or 6 without cirrhosis or with compensated cirrhosis have been established. Adverse events in patients ages 3 to ≤ 12 years of age with genotype 1, 2, 3, or 4 infections were consistent with those observed in adults with the exception of vomiting, rash, and upper abdominal pain. The safety, pharmacokinetics, and efficacy of glecaprevir/pibrentasvir in pediatric patients ≥ 3 years of age with genotype 1 infection, previously treated with an HCV NS5A inhibitor regimen or NS3/4A protease inhibitor have also been established.

Safety and efficacy of ledipasvir/sofosbuvir (Harvoni) have not been established in pediatric patients ≤ 3 years of age. The safety, pharmacokinetics, and efficacy of ledipasvir/sofosbuvir in pediatric patients ≥ 3 years of age with genotype 1 or 4 infection who are treatment-naïve or treatment-experienced without cirrhosis or with compensated cirrhosis have been established.[154,155] The safety and efficacy of ledipasvir/sofosbuvir for the treatment of HCV genotypes 5 or 6 infection in pediatric patients ≥ 3 years of age without cirrhosis or with compensated cirrhosis is supported by comparable ledipasvir, sofosbuvir, and GS-331007 exposures between adults and pediatrics with HCV genotype 1 and similar efficacy and exposures across HCV genotypes 1, 4, 5, and 6 in adults. Likewise, similar exposure data was used to extrapolate the use of ledipasvir/sofosbuvir (Harvoni) in pediatric patients with HCV genotype 1 infection and decompensated cirrhosis (Child-Pugh B or C) and pediatric patients with HCV genotypes 1 and 4 infection who have received a liver transplant without cirrhosis or with compensated cirrhosis.

Safety and efficacy of sofosbuvir/velpatasvir (Epclusa) have been established in treatment-naïve or treatment-experienced pediatric patients ≥ 3 years of age without cirrhosis or with compensated cirrhosis with genotypes 1, 2, 3, 4, and 6. No clinically meaningful differences in pharmacokinetics in pediatric patients were observed in comparison to those observed in adult patients. The safety and efficacy were comparable with those observed in adults. The safety and efficacy in pediatric patients ≥ 3 years of age without cirrhosis or with compensated cirrhosis with genotype 5 are supported by sofosbuvir, GS-331007, and velpatasvir exposures in adults and pediatric patients. A similar rationale is used to support dosing recommendations for pediatric patients with HCV genotype 1, 2, 3, 4, 5, or 6 infection who have decompensated cirrhosis (Child-Pugh B or C).

The safety and efficacy of elbasvir/grazoprevir (Zepatier) have not been established in pediatric patients < 12 years of age who weigh < 30 kg. An open-label study (NCT03379506) assessed the efficacy and safety of elbasvir/grazoprevir in 22 pediatric patients ≥ 12 years to < 18 years of age (median, 13.5 years) for 12 weeks in patients with genotypes 1 (n=21) or 4 (n=1) without cirrhosis who were treatment-naïve (64%) or -experienced (36%); genotype 1a patients with ≥ 1 baseline NS5A RAS were excluded.[156] At baseline, 46% had HCV RNA levels > 800,000 IU/mL, 95% were White, and 50% were female. The overall SVR12 rate was 100%.

Safety and effectiveness of ombitasvir/paritaprevir/ritonavir + dasabuvir (Viekira Pak) and sofosbuvir/velpatasvir/voxilaprevir (Vosevi) have not been established in pediatric patients. The most recent update to the AASLD/IDSA HCV guidelines includes updated recommendations for HCV in children.[157] In regard to testing of perinatally exposed children and siblings of HCV-infected children, AASLD/IDSA recommends that all children born to HCV-infected women should be tested for HCV infection using an antibody-based test at or after 18 months of age (Class I, Level A). Those who are anti-HCV positive after 18 months old should be tested with an HCV RNA assay after age 3 to confirm chronic hepatitis C infection (Class I, Level A). Testing with an HCV RNA assay can be considered within the first year of life; however, the optimal timing of this test is unknown (Class IIa, Level C) and repetitive testing by HCV RNA is not recommended (Class III, Level A). In addition, siblings of children who acquired chronic

HCV via mother-to-child transmission should be tested for HCV infection using anti-HCV antibody testing (Class I, Level C). HCV-infected children and their caregivers should receive adequate counseling regarding transmission risk and universal precautions. Routine monitoring recommendations, including liver biochemistries, vaccinations, disease severity assessment, and surveillance for comorbid conditions are detailed in the AASLD/IDSA guidelines.

Concerning the treatment of chronic HCV in children, AASLD/IDSA recommends the use of DAAs, if available for the child's age group, in all HCV-infected pediatrics ages ≥ 3 years, regardless of disease severity (Class I, Level B) (Class I, Level B).[158] Nonetheless, the extrahepatic manifestations (e.g., cryoglobulinemia, rashes, glomerulonephritis, advanced fibrosis) should lead to early antiviral therapy to minimize future morbidity and mortality (Class I, Level C). For adolescents ≥ 12 years old or weighing ≥ 35 kg without cirrhosis or with compensated cirrhosis, AASLD/IDSA provides DAA regimen recommendations. For patients ≥ 12 years old or ≥ 45 kg with any genotype who are treatment-naïve or interferon experienced without cirrhosis or with compensated cirrhosis, AASLD/IDSA recommends glecaprevir/pibrentasvir for 8 weeks (Class I, Level B). For patients ≥ 6 years old or weighing ≥ 17 kg with any genotype who are treatment-naïve or interferon-experienced without cirrhosis or with compensated cirrhosis, AASLD/IDSA recommends sofosbuvir/velpatasvir for 12 weeks (Class I, Level B). For patients ≥ 3 years old who are treatment-naive or interferon-experienced with genotype 1, 4, 5, or 6 without cirrhosis or with compensated cirrhosis they recommend ledipasvir/sofosbuvir for 12 weeks (Class I, Level B). Detailed recommendations for pediatric patients who are treatment experienced with a prior DAA are included in the full AASLD/IDSA treatment guidelines.

Pregnancy

Ribavirin tablet is Pregnancy Category X. Ribavirin capsules (generics for Rebetol) were previously assigned Pregnancy Category X; however, labeling was updated in compliance with the Pregnancy and Lactation Labeling Rule (PLLR) and replaced with descriptive text. Ribavirin exposure may cause birth defects and/or death of the exposed fetus. Ribavirin is contraindicated in pregnant women or by men whose female partners are pregnant. AASLD/IDSA guidelines for the treatment of HCV state that females who have used ribavirin should not become pregnant for at least 9 months after discontinuation of ribavirin and sexual partners of ribavirin-treated male patients should not become pregnant for at least 6 months after discontinuation of ribavirin (Class III, Level B).[159]

Peginterferon alfa-2a (Pegasys) was previously assigned Pregnancy Category C; however, labeling was updated in compliance with the Pregnancy and Lactation Labeling Rule (PLLR) and replaced with descriptive text.

Previously, ledipasvir/sofosbuvir (Harvoni), sofosbuvir (Sovaldi), and ombitasvir/paritaprevir/ritonavir + dasabuvir (Viekira Pak) were assigned Pregnancy Category B; however, their labeling was updated in compliance with the PLLR and replaced with descriptive text. No adequate human data are available to establish whether or not they pose a risk to pregnancy outcomes.

Elbasvir/grazoprevir (Zepatier), sofosbuvir/velpatasvir (Epclusa), sofosbuvir/velpatasvir/voxilaprevir (Vosevi), or glecaprevir/pibrentasvir (Mavyret) were not assigned a Pregnancy Category. No adequate human data are available to establish whether or not they pose a risk to pregnancy outcomes.

When dual or triple therapy is utilized, the Pregnancy Category of the most restrictive individual drug used in the combination regimen should be considered.

The most recent update to the AASLD/IDSA HCV guidelines includes recommendations for HCV and pregnancy.[160] All pregnant women should be tested for HCV. They recommend antiviral therapy prior to considering pregnancy, whenever practical and feasible, to reduce the risk of HCV transmission to future offspring (Class I, Level B). However, they recommend against treatment during pregnancy due to lack of efficacy and safety data in this population (Class IIb, Level C). Recommendations for monitoring HCV-infected women during pregnancy are described in the guidelines.

Ethnicity

Several trials have demonstrated African Americans and Latinos are less likely than non-Hispanic whites to respond to dual therapy with interferon and ribavirin.[161,162,163] The reasons for these differences are not known.[164]

Higher elbasvir and grazoprevir plasma concentrations were observed in Asians compared to Caucasians. Asians experienced a higher rate of late ALT elevation in clinical trials; however, no dose adjustment of grazoprevir/elbasvir is recommended based on race/ethnicity.

Coinfected HCV/HIV Patients

HIV infection is independently associated with advanced liver fibrosis and cirrhosis in patients with HCV coinfection. Per the AASLD/IDSA guidelines, patients with HIV/HCV coinfection should be treated and retreated the same as persons without HIV infection, after recognizing and managing interactions with antiviral medications.[165] These guidelines also state that treatment courses < 12 weeks, such as ledipasvir/sofosbuvir (Harvoni) for 8 weeks, are not recommended for coinfected patients (Class IIb, Level C). Differences in treatment regimens in co-infected patients are available in the Dosages section.

Patients Who Have Not Responded, Who Have Partially Responded, or Who Have Relapsed Following Initial Treatment

There are 3 classifications used for patients who have received previous therapy for chronic HCV but who failed treatment. Those whose HCV RNA level did not decline by at least 2-$\log_{10}$ IU/mL by treatment week 12 are classified as null responders. Those whose HCV RNA level had dropped by at least 2-$\log_{10}$ IU/mL at week 12, but still had detectable HCV RNA at week 24, are classified as partial responders. Relapsers are defined as patients who have had undetectable HCV RNA during therapy and then develop measurable HCV RNA after the completion of therapy.

As noted in the Overview section, the AASLD/IDSA guidelines include recommendations for treating patients who relapsed after prior therapy.[166]

Renal Impairment[167]

HCV infection is a major health problem in patients with end stage renal disease (ESRD). The incidence of acute HCV infection during maintenance dialysis is much higher than that in the general population because of the risk of nosocomial transmission.[168]

According to the prescribing information, peginterferon alfa-2a (Pegasys) dosage should be reduced to 135 mcg once weekly in patients with a CrCl < 30 mL/minute, including those with ESRD and those on hemodialysis. Signs and symptoms of toxicity should be closely monitored and, if severe or if laboratory abnormalities develop, the dose may be reduced to 90 mcg until symptoms abate. There are no data available on dosage adjustments for renal failure in pediatric patients.

The recommended dosage for ribavirin (generics for Copegus) in patients with renal impairment is as follows: for CrCl 30 to 50 mL/minute, alternating doses of 200 mg and 400 mg every other day; for CrCl < 30 mL/minute and those on hemodialysis, 200 mg daily. The prescribing information for ribavirin (generics for Rebetol) states that ribavirin should not be used in patients with a CrCl < 50 mL/minute.

No dosage adjustment of ombitasvir/paritaprevir/ritonavir + dasabuvir (Viekira Pak) is required for patients with mild, moderate, or severe renal impairment. These agents have not been studied in patients with ESRD or those on hemodialysis. Likewise, no dosage adjustment is recommended for patients taking elbasvir/grazoprevir (Zepatier), or glecaprevir/pibrentasvir (Mavyret) with any degree of renal impairment.

No dosage adjustments are required for ledipasvir/sofosbuvir (Harvoni) and sofosbuvir/velpatasvir/voxilaprevir (Vosevi) in patients with any degree of renal impairment, including those with ESRD on dialysis.

No dosage adjustment of sofosbuvir (Sovaldi) is required for patients with mild to moderate renal impairment (CrCl ≥ 30mL/min); however, sofosbuvir is not recommended in patients with severe renal impairment (CrCl < 30 mL/min) or patients who require hemodialysis because no dosing data are currently available for this patient population.

No dosage adjustment of sofosbuvir/velpatasvir (Epclusa) is recommended for patients with mild, moderate, or severe renal impairment, including ESRD requiring dialysis. No safety data are available in patients with both severe renal impairment and decompensated cirrhosis, including ESRD requiring dialysis. Additionally, no safety data are available in pediatric patients with renal impairment.

The AASLD/IDSA guidelines do not recommend a dose adjustment with any of the DAAs when using recommended regimens as elbasvir, grazoprevir, and ledipasvir are primarily metabolized hepatically and undergo minimal renal elimination (Class I, Level A for CKD stage 1, 2, or 3 and Class IIa, Level B for CKD 4 or 5). Sofosbuvir regimens have demonstrated safety in patients with eGFR < 30 mL/min and the FDA amended package inserts to allow use in patients with renal disease, including those with an eGFR ≤ 30 mL/min and those on dialysis.

Kidney Transplant

The most recent update to the AASLD/IDSA HCV guidelines includes recommendations for treating patients with kidney transplant.[169] For treatment-naïve or non-DAA-experienced kidney transplant with any genotype without cirrhosis or with compensated cirrhosis, they recommend glecaprevir/pibrentasvir (Class I, Level A without cirrhosis; Class IIa, Level C in compensated cirrhosis) or sofosbuvir/velpatasvir for 12 weeks (Class IIa, Level C). For genotype 1, 4, 5, or 6 kidney transplant patients who are treatment naïve or non-DAA-experienced they recommend ledipasvir/sofosbuvir (Class I, Level A) for 12 weeks. An alternative regimen in this same population with genotype 1 or 4 is elbasvir/grazoprevir for 12 weeks in patients without baseline NS5A RASs for elbasvir(Class I, Level B). For DAA-experienced kidney transplant patients with any genotype with or without compensated cirrhosis, they recommend sofosbuvir/velpatasvir/voxilaprevir with or without ribavirin (based on whether the patient has cirrhosis and multiple negative baseline characteristics) for 12 weeks (Class IIa, Level C).

Hepatic Impairment[170]

Peginterferon alfa-2a + ribavirin should be discontinued in patients who develop hepatic decompensation during treatment.

No dosage adjustment of ledipasvir/sofosbuvir (Harvoni) is required for patients with mild, moderate, or severe hepatic impairment (Child-Pugh A, B or C). Clinical and hepatic laboratory monitoring are recommended in patients with decompensated cirrhosis as clinically indicated.

No dosage adjustment of ombitasvir/paritaprevir/ritonavir + dasabuvir (Viekira Pak) is required for patients with mild hepatic impairment (Child-Pugh A). Viekira Pak is contraindicated in patients with moderate and severe hepatic impairment (Child-Pugh B and C).

No dose adjustment of sofosbuvir (Sovaldi) is required for patients with mild, moderate, or severe hepatic impairment (Child-Pugh A, B, or C).

No dosage adjustment of grazoprevir/elbasvir (Zepatier) is recommended in patients with mild hepatic impairment (Child-Pugh A). Grazoprevir/elbasvir is contraindicated in patients with moderate hepatic impairment (Child-Pugh B) and severe hepatic impairment (Child-Pugh C) or those with any history of hepatic decompensation. The safety and efficacy of grazoprevir/elbasvir have not been established in patients awaiting liver transplant or in liver transplant recipients.

No dosage adjustment of sofosbuvir/velpatasvir is required for patients with mild, moderate, or severe hepatic impairment (Child-Pugh A, B, or C). Clinical and hepatic laboratory monitoring (including direct bilirubin), as clinically indicated, is recommended for patients with decompensated cirrhosis receiving treatment with sofosbuvir/velpatasvir and ribavirin.

Safety and efficacy of sofosbuvir (Sovaldi) have not been established in patients with decompensated cirrhosis.

No dosage adjustment of sofosbuvir/velpatasvir/voxilaprevir (Vosevi) is required for patients with mild hepatic impairment (Child-Pugh A). The safety and efficacy have not been established in patients with moderate or severe hepatic impairment (Child-Pugh B or C) and the combination is not recommended in these patients. Use of sofosbuvir/velpatasvir/voxilaprevir is not recommended in patients with moderate to severe hepatic impairment (Child-Pugh B or C) or those with any history of prior hepatic decompensation due to the risk of hepatic decompensation or failure in patients with evidence of advanced liver disease. Discontinue therapy in patients who develop evidence of hepatic decompensation/failure.

No dosage adjustment of glecaprevir/pibrentasvir (Mavyret) is required in patients with mild hepatic impairment (Child-Pugh A). Safety and efficacy have not been established in patients with moderate hepatic impairment (Child-Pugh B), but due to postmarketing case reports of hepatic complications, the combination is contraindicated in these patients. Glecaprevir/pibrentasvir is also contraindicated in patients with severe hepatic impairment (Child-Pugh C) or those with any history of prior hepatic decompensation.

The AASLD/IDSA guidelines have specific recommendations for patients who have compensated cirrhosis (mild hepatic impairment; Child-Pugh A) and those with decompensated cirrhosis (moderate or severe hepatic impairment; Child-Pugh B or C); the AASLD/IDSA recommendations for patients with compensated cirrhosis are described in the Overview section.[171]

The guidelines state patients with decompensated cirrhosis should be referred to a practitioner with expertise in that condition (ideally in a liver transplant center) (Class I, Level C).[172] The recommended regimen for patients with HCV genotype 1, 4, 5, or 6 who have decompensated cirrhosis (Child-Pugh B or C), including those with hepatocellular carcinoma, and are ribavirin eligible is ledipasvir/sofosbuvir and low initial dose ribavirin for 12 weeks (Class I, Level A). Another recommended regimen for patients with decompensated cirrhosis with any genotype is 12 weeks of sofosbuvir/velpatasvir with weight-based ribavirin in those with Child-Pugh B or low initial dose ribavirin in those with Child-Pugh C (Class I, Level A). For patients with HCV genotype 1, 4, 5, or 6 who have decompensated cirrhosis who are ribavirin ineligible, 24 weeks of ledipasvir/sofosbuvir (Class I, Level A) is recommended. Sofosbuvir/velpatasvir is recommended in ribavirin ineligible patients with any genotype (Class I, Level A) for 24 weeks. For patients with HCV genotype 1, 4, 5, or 6 who have decompensated cirrhosis in whom prior sofosbuvir-based treatment has failed, ledipasvir/sofosbuvir plus low initial dose ribavirin for 24 weeks is recommended. For patients of any genotype and decompensated cirrhosis who previously failed sofosbuvir- or NS5A inhibitor-based treatment, 24 weeks of sofosbuvir/velpatasvir plus ribavirin is recommended; patients with Child-Pugh B should receive weight-based ribavirin and those with Child-Pugh C should receive low dose ribavirin (Class II, Level C).

The guidelines further state that patients with decompensated cirrhosis should not receive glecaprevir, grazoprevir, paritaprevir, simeprevir, and voxilaprevir based treatments (Class III, Level B).

Polymorphisms

Testing for polymorphism at the Y93H position of the NS5A HCV protein is recommended for genotype 3 patients without cirrhosis who have failed peginterferon/ribavirin and will begin treatment with sofosbuvir/velpatasvir; if Y93H is present, ribavirin should be included as part of the regimen.

Research demonstrates lower SVR12 rates in genotype 1a-infected patients with 1 or more baseline NS5A RAS at amino acid positions M28, Q30, L31, or Y93. AASLD/IDSA recommends RAS testing for select products when used in patients with HCV genotype 1a.[173] For patients being considered for elbasvir/grazoprevir (Zepatier), NS5A RAS testing is recommended for treatment-naive or -experienced patients (Class I, Level A) to determine the dosage regimen and duration. If polymorphisms are present, a different regimen should be considered (Class I, Level A). For patients being considered for ledipasvir/sofosbuvir (Harvoni), NS5A RAS testing can be considered for genotype 1a-infected, treatment-experienced patients (with or without cirrhosis). If > 100-fold resistance is present, a different recommended therapy should be used (Class I, Level A).

Likewise, AASLD/IDSA also recommends RAS testing for select products when used in patients with HCV genotype 3.[174] NS5A RAS testing is recommended for treatment-experienced patients without cirrhosis and treatment-naive patients with cirrhosis being considered for 12-week sofosbuvir/velpatasvir (Epclusa) therapy (Class 1, Level A). As described in the product labeling, if Y93H is present, AASLD/IDSA concurs that weight-based ribavirin should be added to the regimen, or another recommended regimen should be used. A resistance primer and additional information on the clinical relevance of the various known resistance-associated substitutions are detailed in the guidelines.

Post-Liver Transplantation

The safety and efficacy of peginterferon alfa, alone or in combination with ribavirin for the treatment of chronic HCV infection in liver or other organ transplant recipients have not been established.

The AASLD/IDSA guidelines provide treatment recommendations for treatment-naïve and treatment-experienced patients who develop recurrent HCV after liver transplantation.[175] Patients with any genotype in the allograft who are treatment-naïve or treatment-experienced without cirrhosis are recommended glecaprevir/pibrentasvir or sofosbuvir/velpatasvir for 12 weeks (Class I, Level B). In genotype 1, 4, 5, or 6 infection in the allograft patients who are treatment-naïve or treatment-experienced without cirrhosis the recommended treatment regimen is ledipasvir/sofosbuvir for 12 weeks (Class I, Level B). For those in this population with compensated cirrhosis, the recommended treatment regimen for any genotype is sofosbuvir/velpatasvir (Class I, Level B) or glecaprevir/pibrentasvir (Class I, Level C) for 12 weeks. For those with genotype 1, 4, 5, or 6 another recommended regimen is ledipasvir/sofosbuvir with weight-based ribavirin (Class I, Level A) for 12 weeks. In treatment-naïve or treatment-experienced genotype 1, 4, 5, or 6 infection in the allograft patients with decompensated cirrhosis, the recommended regimen is ledipasvir/sofosbuvir with low initial dose ribavirin for 12 weeks or 24 weeks if treatment experienced (Class I, Level B). For patients in this same population with any genotype, the recommended regimen is sofosbuvir/velpatasvir with ribavirin for 12 weeks or 24 weeks if treatment experienced (Class I, Level B).

The following regimen is not recommended in patients with HCV infection of the allograft with compensated cirrhosis: elbasvir/grazoprevir-based regimens (Class III, Level C). The following regimens are not recommended in patients with HCV infection of the allograft with decompensated cirrhosis: paritaprevir/ombitasvir/ritonavir with or without dasabuvir (Class III, Level B) or elbasvir/grazoprevir-based regimens (Class III, Level C).

Other

No differences in safety or efficacy have been seen in patients aged 65 and over; therefore, no dose adjustment of sofosbuvir (Sovaldi) is warranted in geriatric patients.

A higher rate of late ALT elevation was observed in subjects aged 65 years and older in clinical trials with elbasvir/grazoprevir (Zepatier); however, no dosage adjustment of grazoprevir/elbasvir is recommended in geriatric patients.

Higher elbasvir and grazoprevir plasma concentrations were observed in females compared to males. Females experienced a higher rate of late ALT elevation in clinical trials; however, no dose adjustment of grazoprevir/elbasvir is recommended based on gender.

HCV-infected patients, regardless of genotype, with hepatocellular carcinoma meeting the Milan criteria (defined as the presence of a tumor 5 cm or less in diameter in patients with single hepatocellular carcinomas and no more than 3 tumor nodules, each 3 cm or less in diameter in patients with multiple tumors and no extrahepatic manifestations of the cancer or evidence of vascular invasion of the tumor) have been treated with sofosbuvir 400 mg and weight-based ribavirin daily for 24 to 48 weeks or until the time of liver transplantation, whichever occurred first. The primary endpoint of post-transplant virologic response (pTVR) defined as HCV RNA less than the lower limit of quantification (LLOQ) at 12 weeks post-transplant, was met in 64% of evaluable subjects who had reached the 12-week, post-transplant time point. The safety profile of sofosbuvir and ribavirin in HCV-infected patients prior to liver transplantation was comparable to that observed in subjects treated with sofosbuvir and ribavirin in phase 3 clinical trials.

DOSAGES[176,177,178,179,180,181,182,183,184,185,186,187,188,189,190]

Combination Therapy

The AASLD/IDSA guidelines recommend combination therapy for the treatment of all HCV patients. Elbasvir/grazoprevir (Zepatier), ledipasvir/sofosbuvir (Harvoni), ombitasvir/paritaprevir/ritonavir + dasabuvir (Viekira Pak), sofosbuvir (Sovaldi), sofosbuvir/velpatasvir (Epclusa), sofosbuvir/velpatasvir/voxilaprevir (Vosevi), and glecaprevir/ pibrentasvir (Mavyret) dosing does not involve response-guided therapy. Other factors influencing the choice of agent, as well as the duration of therapy, include HCV genotype, whether the patient has cirrhosis, whether or not the patient is interferon/ribavirin intolerant, and whether the patient is treatment-naïve or has been previously treated.

Drug	Dosage	Duration of Therapy	Availability
Peginterferon Dual Combination Therapy			
peginterferon alfa-2a (Pegasys) + ribavirin	Genotypes 1, 4: 180 mcg SC once weekly plus oral ribavirin (1,000 mg per day if < 75 kg or 1,200 mg per day if ≥ 75 kg)	48 weeks	SDV: 180 mcg/1 mL Prefilled syringe: 180 mcg/0.5 mL (may self-inject after proper training)
	Genotypes 2, 3: 180 mcg SC once weekly plus ribavirin 400 mg orally twice daily	24 weeks	
	Coinfection with HIV (regardless of genotype): 180 mcg SC once weekly plus ribavirin 400 mg orally twice daily	48 weeks	
	Age 5 to 17 years: 180 mcg/1.73 m^2 SC once weekly plus ribavirin 15 mg/kg/day orally with food in 2 divided doses	Genotype 1: 48 weeks	
		Genotypes 2 and 3: 24 weeks	
Peginterferon Triple Combination Therapy			
sofosbuvir (Sovaldi) + peginterferon/ ribavirin	400 mg orally once daily plus weight-based oral ribavirin and SC weekly peginterferon Dosage reductions are not recommended Ribavirin dosing in adults: ▪ < 75 kg: 1,000 mg/day ▪ ≥ 75 kg: 1,200 mg/day	Genotype 1 or 4: 12 weeks	sofosbuvir 400 mg tablet (additional strengths and formulations approved for other regimens) 150 mg, 200 mg, fixed dose oral pellets in a packet

Dosages (continued)

Drug	Dosage	Duration of Therapy	Availability
Oral Combination Therapy			
elbasvir/ grazoprevir (Zepatier) ± ribavirin	Fixed-dose combination: elbasvir 50 mg/grazoprevir 100 mg orally once daily with or without food and with or without oral ribavirin Ribavirin should be added to the regimen for genotype 1a treatment-naïve or PegIFN/RBV-experienced patients with baseline NS5A polymorphisms, genotype 1a or 1b who are PegIFN/RBV/NS3/4A PI-experienced, and genotype 4 patients who are PegIFN/RBV-experienced Ribavirin dosing: weight based (range, 800 to 1,200 mg/day) administered orally in 2 divided doses with food; dosing adjusted for renal impairment	Genotype 1a (without baseline NS5A polymorphisms)* or 1b– treatment-naïve, PegIFN/RBV-experienced, PegIFN/RBV/NS3/4A PI-experienced: 12 weeks Genotype 1a (with baseline NS5A polymorphisms)*– treatment-naïve or PegIFN/RBV-experienced: 16 weeks† Genotype 4– treatment-naïve: 12 weeks Genotype 4– PegIFN/RBV-experienced: 16 weeks	elbasvir/ grazoprevir 50/100 mg fixed-dose tablet

* Testing for the presence of virus with NS5A resistance-associated polymorphisms in genotype 1a patients is recommended prior to initiating grazoprevir/elbasvir. SVR12 rates were lower in genotype 1a-infected patients with 1 or more baseline NS5A resistance-associated polymorphisms at amino acid positions 28, 30, 31, or 93.

† The optimal grazoprevir/elbasvir-based treatment regimen and duration of therapy for PegIFN/RBV/PI-experienced genotype1a-infected patients with 1 or more baseline NS5A resistance-associated polymorphisms at positions 28, 30, 31, and 93 has not been established.

Dosages (continued)

Drug	Dosage	Duration of Therapy	Availability
Oral Combination Therapy *(continued)*			
glecaprevir/ pibrentasvir (Mavyret)	Fixed-dose combination in adults and pediatric patients ≥ 12 years old ≥ 45 kg: 3 glecaprevir 100 mg/pibrentasvir 40 mg tablets orally once daily with food at the same time daily Pediatric patients 3 to < 12 years old < 45 kg: (oral pellets) ▪ < 20 kg: 150 mg/60 mg/day ▪ 20 kg to < 30 kg: 200 mg/80 mg/day ▪ 30 kg to < 45 kg: 250 mg/100 mg/day	Genotypes 1, 2, 3, 4, 5, and 6 (treatment-naïve without cirrhosis or with compensated cirrhosis [Child-Pugh A]): 8 weeks Genotype 1 (treatment-experienced patient without cirrhosis or with compensated cirrhosis previously treated with a regimen containing an NS5A without prior treatment with an NS3/4A PI): 16 weeks Genotype 1 (treatment-experienced patient without cirrhosis or with compensated cirrhosis previously treated with a regimen containing an NS3/4A PI without prior treatment with an NS5A inhibitor): 12 weeks Genotype 1, 2, 4, 5 or 6 (treatment-experienced patient without cirrhosis previously treated with a regimen containing pegylated interferon, ribavirin, and/or sofosbuvir) (PRS): 8 weeks Genotype 1, 2, 4, 5 or 6 (treatment-experienced patient with compensated cirrhosis previously treated with a regimen containing pegylated interferon, ribavirin, and/or sofosbuvir) (PRS): 12 weeks Genotype 3 (treatment-experienced patient without cirrhosis or with compensated cirrhosis previously treated with a regimen containing pegylated interferon, ribavirin, and/or sofosbuvir) (PRS): 16 weeks Liver or kidney transplant: 12 weeks with a 16-week regimen for GT 1-infected patients who are NS5A inhibitor-experienced without prior treatment with an NS3/4A protease inhibitor or in GT 3-infected patients who are PRS treatment-experienced Dosing is the same regardless of HIV coinfection	100/40 mg fixed-dose tablet 50 mg/20 mg fixed dose oral pellets in a packet

Dosages (continued)

Drug	Dosage	Duration of Therapy	Availability
Oral Combination Therapy *(continued)*			
ledipasvir/sofosbuvir (Harvoni) ± ribavirin	Fixed-dose combination in adults: ledipasvir 90 mg/ sofosbuvir 400 mg orally once daily at a regularly scheduled time with or without oral ribavirin Pediatrics (using pellets or tablets): ▪ ≥ 35 kg: 90/400 mg/day ▪ 17 to 35 kg: 45/200 mg/day ▪ < 17 kg 33.75/150 mg/day (pellets only) Ribavirin should be added to the regimen for genotype 1 treatment-naïve and treatment-experienced patients with decompensated cirrhosis (Child-Pugh B or C) Ribavirin should be added to the regimen for genotype 1 or 4 patients treatment-naïve and treatment-experienced liver transplant recipients with compensated (Child-Pugh A) cirrhosis or without cirrhosis Ribavirin dosing (adults): ▪ Noncirrhotic or Child-Pugh A cirrhosis post-transplantation: 1,000 mg/day orally for patients < 75 kg and 1,200 mg orally for patients ≥ 75 kg ▪ Child-Pugh B or C: 600 mg orally once daily and increasing to 1,000 mg/day or 1,200 mg/day weight-based dosing as tolerated Ribavirin dosing (pediatrics): ▪ ≥ 80 kg: 1,200 mg/day ▪ 66 to 80 kg: 1,000 mg/day ▪ 50 to 65 kg: 800 mg/day ▪ 47 to 49 kg: 600 mg/day ▪ < 47 kg: 15 mg/kg/day	Genotype 1 – treatment-naïve (with compensated cirrhosis [Child-Pugh A] or without cirrhosis): 12 weeks‡ Genotype 1 – treatment-experienced (without cirrhosis):§ 12 weeks Genotype 1 – treatment-experienced with compensated cirrhosis:§ 24 weeks¶ Genotype 1 – treatment-naïve or experienced (with decompensated cirrhosis): 12 weeks with ribavirin Genotype 1 or 4 – treatment-naïve or experienced§ liver transplant recipients (with compensated cirrhosis or without cirrhosis): 12 weeks with ribavirin Genotypes 4, 5, or 6 – treatment-naïve or treatment-experienced§ with compensated cirrhosis or without cirrhosis: 12 weeks Patients coinfected with HIV/HCV should be treated in the same manner described above Genotype 1 – treatment-naïve pediatric patients without cirrhosis or with compensated cirrhosis: 12 weeks Genotype 1 – treatment-experienced‖ pediatric patients without cirrhosis: 12 weeks Genotype 1 – treatment-experienced‖ pediatric patients with compensated cirrhosis: 24 weeks Genotype 4, 5, or 6 – treatment-naïve or treatment-experienced‖ pediatric patients without cirrhosis or with compensated cirrhosis: 12 weeks	45/200 mg (brand only), 90/400 mg fixed-dose tablet 33.75/150 mg, 45/200 mg fixed dose oral pellets in a packet (brand only)

‡ Treatment with 8 weeks of ledipasvir/sofosbuvir can be considered for treatment-naïve patients without cirrhosis who have a baseline HCV RNA less than 6 million IU/mL.

§ Treatment-experienced patients include those who have failed a PegIFN/RBV based regimen with or without an HCV protease inhibitor.

¶ A 12-week regimen with ribavirin may be considered in treatment-experienced patients who are eligible for ribavirin.

‖ Treatment-experienced patients include those who have failed a PegIFN/RBV based regimen

Dosages (continued)

Drug	Dosage	Duration of Therapy	Availability
Oral Combination Therapy *(continued)*			
ombitasvir/ paritaprevir/ritonavir plus dasabuvir (Viekira Pak) ± ribavirin[**,††]	Combination: 2 ombitasvir/paritaprevir/ritonavir 12.5/75/50 mg tablets orally once daily (in the morning) and 1 dasabuvir 250 mg tablet orally twice daily (morning and evening) with a meal ± weight-based oral ribavirin (< 75 kg = 1,000 mg and ≥ 75 kg = 1,200 mg)	Genotype 1a (without cirrhosis): 12 weeks in combination with ribavirin Genotype 1a (with compensated cirrhosis): 24 weeks in combination with ribavirin[‡‡] Genotype 1b (without cirrhosis or with compensated cirrhosis): 12 weeks	ombitasvir/ paritaprevir/ ritonavir 12.5/75/50 mg fixed-dose tablet; dasabuvir 250 mg tablet
sofosbuvir (Sovaldi) + ribavirin	sofosbuvir 400 mg orally once daily at a regularly scheduled time plus weight-based oral ribavirin Sofosbuvir dosing in pediatrics (using pellets or tablets): ▪ ≥ 35 kg: 400 mg/day ▪ ≥ 17 to < 35 kg: 200 mg/day ▪ < 17 kg: 150 mg/day Dosage reductions are not recommended Ribavirin dosing in adults: ▪ < 75 kg: 1,000 mg/day ▪ ≥ 75 kg: 1,200 mg/day Ribavirin dosing in pediatrics: ▪ < 47 kg: 15 mg/kg/day ▪ 47 to 49 kg: 600 mg/day ▪ 50 to 65 kg: 800 mg/day ▪ 66 to 80 kg: 1,000 mg/day ▪ ≥ 80 kg: 1,200 mg/day	Genotype 2: 12 weeks Genotype 3: 24 weeks Patients with hepatocellular carcinoma awaiting liver transplantation: up to 48 weeks or until time of liver transplant Genotype 1 patients who are interferon ineligible: 24 weeks HCV/HIV-1 coinfected patients with genotype 2: 12 weeks HCV/HIV-1 coinfected patients with genotype 3: 24 weeks Genotype 2 (pediatric patients ≥ 12 years of age or ≥ 35 kg): 12 weeks Genotype 3 (pediatric patients ≥ 12 years of age or ≥ 35 kg): 24 weeks	sofosbuvir 200 mg, 400 mg tablet 150 mg, 200 mg fixed dose oral pellets in a packet

** Viekira Pak: Follow the genotype 1a dosing recommendations in patients with an unknown genotype 1 subtype or with mixed genotype 1 infection

†† Viekira Pak: For patients with HCV/HIV-1 coinfection, follow the dosage recommendations per genotype. In liver transplant recipients with normal hepatic function and mild fibrosis (Metavir fibrosis score ≤2), the recommended duration of Viekira Pak with ribavirin is 24 weeks.

‡‡ Viekira Pak administered with ribavirin for 12 weeks may be considered for some patients based on prior treatment history (however, patients who were prior null responders to peginterferon/RBV had more virologic failures on 12-week regimen).

Dosages (continued)

Drug	Dosage	Duration of Therapy	Availability
Oral Combination Therapy *(continued)*			
sofosbuvir/velpatasvir (Epclusa) ± ribavirin	Fixed-dose combination in adults: sofosbuvir 400 mg/velpatasvir 100 mg orally once daily with or without food and with or without oral ribavirin Ribavirin should be added to the regimen for patients with decompensated cirrhosis Ribavirin dosing is weight based: 1,000 mg for patients < 75 kg and 1,200 mg/day for patients ≥ 75 kg divided and administered orally twice daily with food Pediatric patients ≥ 3 years of age: ▪ < 17 kg: 150 mg/37.5 mg/day ▪ 17 to < 30 kg: 200 mg/50 mg/day ▪ > 30 kg: 400 mg/100 mg/day Pediatric patients < 6 years of age, administer oral pellets with food Ribavirin dosing in pediatrics: ▪ < 47 kg: 15 mg/kg/day ▪ 47 to 49 kg: 600 mg/day ▪ 50 to 65 kg: 800 mg/day ▪ 66 to 80 kg: 1,000 mg/day ▪ ≥ 80 kg: 1,200 mg/day	Genotypes 1, 2, 3, 4, 5, and 6 (without cirrhosis or with compensated cirrhosis): 12 weeks Genotypes 1, 2, 3, 4, 5, and 6 (with decompensated cirrhosis): 12 weeks in combination with ribavirin Genotypes 1, 2, 3, 4, 5, and 6 (liver transplant recipients without cirrhosis or with compensated cirrhosis): 12 weeks Dosing is the same regardless of HIV co-infection	sofosbuvir/velpatasvir 400/100 mg, 200/50 mg (brand only) fixed-dose tablet 150 mg/37.5 mg, 200 mg/50 mg fixed dose oral pellets in a packet
sofosbuvir/velpatasvir/voxilaprevir (Vosevi)	Fixed-dose combination: sofosbuvir 400 mg/velpatasvir 100 mg/voxilaprevir 100 mg orally once daily with a meal	Genotypes 1, 2, 3, 4, 5, and 6 (treatment-experienced patients previously been treated with an HCV regimen containing an NS5A inhibitor): 12 weeks Genotypes 1a or 3 (treatment-experienced patients previously treated with an HCV regimen containing sofosbuvir without an NS5A inhibitor): 12 weeks	400/100/100 mg fixed-dose tablet

Sofosbuvir (Sovaldi) and ledipasvir/sofosbuvir (Harvoni) pellets should not be chewed; they should be administered with food, sprinkling the pellets on ≥ 1 spoonful of non-acidic soft food (e.g., pudding, mashed potatoes, ice cream, chocolate syrup) at or below room temperature. Take within 30 minutes, gently mixing with food and swallowing entire contents without chewing.

Sofosbuvir/velpatasvir (Epclusa) pellets should not be chewed; they should be administered with food, sprinkling the pellets on ≥ 1 spoonful of non-acidic soft food (e.g., pudding, chocolate syrup, ice cream) at or below room temperature. Take within 15 minutes, gently mixing with food and swallowing entire contents.

Glecaprevir/pibrentasvir (Mavyret) pellets should be taken together and not be chewed; they should be administered with food, sprinkling pellets on small amount of soft food (e.g., peanut butter, chocolate hazelnut spread, cream cheese, thick jam, or Greek yogurt) with a low water content that will stick to a spoon. Take within 15 minutes, gently mixing with food and swallowing entire contents. It is not recommended to take with liquids or foods that slide off the spoon due to the drug potentially dissolving quickly and becoming less effective.

ribavirin

Drug	Adult Dosage	Availability
ribavirin tablet	As listed above for combination therapy	Tablet: 200 mg (generic only)
ribavirin capsule		Capsule: 200 mg (generic only)

Dose modifications may be necessary due to adverse effects such as neutropenia, thrombocytopenia, depression, progressive increases in ALT values over baseline, and impaired renal function. Consult prescribing information for dosage adjustments.

Recommended dosing of ribavirin in adolescents by AASLD/IDSA is weight-based, as follows: 15 mg/kg/day for those < 47 kg, 600 mg/day for 47 to 49 kg, 800 mg/day for 50 to 65 kg, 1,000 mg/day for 66 to 80 kg, and 1,200 mg/day for > 80 kg.[191]

CLINICAL TRIALS

Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all drugs in this class and chronic hepatitis C for the FDA-approved indications. Randomized, controlled comparative trials are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Due to the chronic nature, course of disease progression, and treatment duration for hepatitis C, many clinical trials lack blinding. Open-label trials have been included below upon initial approval in the absence of blinded studies. Studies performed in the US were given preference since genotype 1 is most common in the US and has been associated with lower SVR. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

Studies of peginterferon alfa-2a (Pegasys) with ribavirin demonstrated efficacy but they have been removed from this review (including use in pediatrics) since they are no longer considered the standard of care.[192,193,194,195,196,197,198]

elbasvir/grazoprevir (Zepatier) in genotypes 1 and 4

The efficacy of grazoprevir/elbasvir in treatment-naïve patients with genotype 1 chronic HCV with or without cirrhosis was demonstrated in the C-EDGE TN (n=382) and C-EDGE COINFECTION (n=189) trials.[199,200] Grazoprevir/elbasvir was administered orally once daily in these trials. C-EDGE TN was a phase 3, randomized, double-blind, placebo-controlled trial in treatment-naïve patients with genotype 1 or 4 infection with or without cirrhosis. Subjects received grazoprevir/elbasvir for 12 weeks. Among patients with genotype 1 infection, 55% had genotype 1a and 45% had genotype 1b. SVR was the primary endpoint in all trials and was defined as HCV RNA less than lower limit of quantification (LLOQ) at 12 weeks after the cessation of treatment (SVR12). Overall, SVR12 was achieved in 95% of patients following 12 weeks of treatment, 92% in genotype 1a, 98% in genotype 1b, 94% in the non-cirrhotic patients, and 97% in the cirrhotic patients. C-EDGE COINFECTION was an open-label, single-arm trial in treatment-naïve HCV/HIV-1 co-infected patients with genotype 1 or 4 infection with or without cirrhosis. Subjects received grazoprevir/elbasvir for 12 weeks. Among subjects with genotype 1 infection, 76% had genotype 1a, 23% had genotype 1b, and 1% had genotype 1-other chronic HCV infection. Overall, SVR12 was achieved in 95% of patients following 12 weeks of treatment, 94% in genotype 1a, 96% in genotype 1b, 94% in the non-cirrhotic patients, and 100% in the cirrhotic patients.

The efficacy of grazoprevir/elbasvir in treatment-experienced patients who failed prior pegylated-interferon (PegIFN) with RBV therapy with genotype 1 chronic HCV with or without cirrhosis was demonstrated in the C-EDGE TE (n=377).[201] C-EDGE TE was a randomized, open-label comparative trial in subjects with genotype 1 or 4 infection, with or without cirrhosis, with or without HCV/HIV-1 coinfection, who had failed prior therapy with PegIFN + RBV therapy. Subjects were randomized in a 1:1:1:1 ratio to 1 of the following treatment groups: grazoprevir/elbasvir for 12 weeks, grazoprevir/elbasvir for 16 weeks, grazoprevir/elbasvir plus RBV for 12 weeks, or grazoprevir/elbasvir plus RBV for 16 weeks. Grazoprevir/elbasvir was administered orally once daily and the RBV dosage was weight-based and administered orally in 2 divided doses with food. SVR was the primary endpoint. SVR12 was achieved in 94% of patients following 12 weeks of treatment and 97% following 16 weeks of treatment. An SVR12 rate of 90% was achieved in patients with genotype 1a and 100% in patients with genotype 1b treated for 12 weeks. An SVR12 rate of 95% was achieved in patients with genotype 1a and 100% in patients with genotype 1b treated for 16 weeks.

The efficacy of grazoprevir/elbasvir in patients with genotype 4 chronic HCV infection was demonstrated in the C-EDGE trial described above (C-EDGE TN [n=26], C-EDGE COINFECTION [n=28], and C-EDGE TE [n=37]) and C-SCAPE (n=20).[202] C-SCAPE was a randomized, open-label trial of genotype 4 patients without cirrhosis in which patients were randomized in a 1:1 ratio to elbasvir/grazoprevir once daily for 12 weeks with or without ribavirin. Grazoprevir/elbasvir was administered orally once daily and the RBV dosage was weight-based and administered orally in 2 divided doses with food. SVR was the primary endpoint. In C-SCAPE, C-EDGE TN, and C-EDGE COINFECTION trials combined, 64% were treatment-naïve; 22% had cirrhosis; and 30% had HCV/HIV-1 coinfection. The SVR12 rate among subjects treated with grazoprevir/elbasvir for 12 weeks was 97%. In C-EDGE TE, a total of 37 genotype 4 treatment-experienced subjects received a 12- or 16-week grazoprevir/elbasvir with or without RBV regimen. The SVR12 rate among randomized patients treated with grazoprevir/elbasvir + RBV for 16 weeks was 100%.

elbasvir/grazoprevir (Zepatier) in treatment-experienced patients, including a protease inhibitor, with genotype 1 infection

The efficacy of grazoprevir/elbasvir in treatment-experienced patients with genotype 1 chronic HCV with or without cirrhosis who failed prior PegIFN with RBV and a protease inhibitor therapy was demonstrated in the C-SALVAGE (n=79).[203] C-SALVAGE was an open-label single-arm trial in subjects with genotype 1 infection, with or without cirrhosis, who had failed prior treatment with boceprevir, simeprevir, or telaprevir in combination with PegIFN + RBV. Subjects received grazoprevir/elbasvir + RBV for 12 weeks. Grazoprevir/elbasvir was administered orally once daily and the RBV dosage was weight-based and administered orally in 2 divided doses with food. SVR was the primary endpoint. Among these subjects, 43% had cirrhosis and 46% had baseline NS3 resistance-associated substitutions. Overall, SVR12 was achieved in 96% of subjects. Treatment outcomes were consistent in genotype 1a and genotype 1b subjects, in subjects with different response to previous HCV therapy, and in subjects with or without cirrhosis. Treatment outcomes were generally consistent in subjects with or without NS3 resistance-associated substitutions at baseline, although limited data are available for subjects with specific NS3 resistance-associated substitutions.

elbasvir/grazoprevir (Zepatier) in genotype 1 infection with severe renal impairment

The efficacy of grazoprevir/elbasvir in patients with genotype 1 HCV and severe renal impairment, including those on hemodialysis, was demonstrated in C-SURFER (n=235).[204,205] C-SURFER was a randomized, double-blind, placebo-controlled trial in subjects with genotype 1 infection, with or without cirrhosis, with CKD stage 4 (eGFR 15 to 29 mL/min/1.73 m^2) or CKD stage 5 (eGFR < 15 mL/min/1.73 m^2), including subjects on hemodialysis, who were treatment-naïve or who had failed prior therapy with IFN or PegIFN ± RBV therapy. Subjects were randomized in a 1:1 ratio to 1 of the following treatment groups: grazoprevir/elbasvir for 12 weeks (treatment group) or placebo for 12 weeks. Overall, an SVR12 was achieved in 94% of patients, 97% in genotype 1a, 92% in genotype 1b, 93% in dialysis patients, and 100% and 93% in patients with CKD stages 4 and 5, respectively.

glecaprevir/pibrentasvir (Mavyret) in genotypes 1, 2, 3, 4, 5, and 6 treatment-naïve and treatment-experienced patients without cirrhosis or with compensated cirrhosis

The efficacy of glecaprevir/pibrentasvir was studied in 8 phase 2 and 3 trials in 2,152 subjects diagnosed with HCV genotypes 1 through 6 with or without compensated cirrhosis who were either treatment-naïve or treatment-experienced.[206] Primary endpoint for each trial was the proportion of patients who achieved SVR, defined as HCV RNA less than lower limit of quantification (LLOQ) at 12 weeks after stopping study treatment (SVR12). Across the various trials, the median age of enrolled patients was 54 years old, 73% of patients were treatment-naïve, 54% of patients were male, 12% of patients had cirrhosis, and 60% of patients were either genotype 1 or 2.

ENDURANCE-1 was a randomized, open-label, multicenter trial which compared glecaprevir/pibrentasvir 300 mg/120 mg administered daily for 8 weeks versus 12 weeks in patients who were treatment-naïve or treatment-experienced with pegylated interferon + ribavirin ± sofosbuvir (PRS), but did not have cirrhosis, and were diagnosed with HCV genotype 1 with or without HIV (n=703).[207,208] The results showed that the SVR12 for the 8-week group was 99%.

ENDURANCE-3 was a randomized, active-controlled, multicenter trial which compared 8 weeks of glecaprevir/pibrentasvir 300 mg/120 mg daily with 12 weeks of glecaprevir/pibrentasvir 300 mg/120 mg

daily and 12 weeks of sofosbuvir (SOF) 400 mg + daclatasvir (DCV) 60 mg daily in patients with HCV genotype 3 who were treatment-naïve and non-cirrhotic (n=505).[209,210] The primary endpoint was non-inferiority compared to SOF + DCV. The results showed that SVR12 was 95% in both arms of glecaprevir/pibrentasvir, compared to 97% for SOF + DCV. This confirmed that the 12-week treatment was non-inferior to SOF + DCV, and the 8-week treatment was non-inferior to the 12-week treatment. DCV is no longer commercially available in the US.

ENDURANCE-4 and SURVEYOR-1 were open-label, multicenter trials which measured the efficacy of glecaprevir/pibrentasvir 300 mg/120 mg daily treatment for 12 weeks in patients with HCV genotypes 5, and 6 who were treatment-naïve or treatment-experienced with PRS but did not have cirrhosis (n=57). The SVR12 rate was 100% in both genotypes 5 and 6.

EXPEDITION-1 and EXPEDITION-4 were open-label, multicenter trials that measured the efficacy of glecaprevir/pibrentasvir 300 mg/120 mg administered daily for 12 weeks in patients who were treatment-naïve or treatment-experienced with PRS and with or without cirrhosis (n=250).[211,212,213] EXPEDITION-1 enrolled patients with HCV genotypes 1, 2, 4, 5, and 6 with HIV. EXPEDITION-4 enrolled patients diagnosed with all genotypes who had severe renal impairment or end-stage renal disease (ESRD). The SVR12 rate was 99% in EXPEDITION-1 and 98% in EXPEDITION-4.

EXPEDITION-2 was a phase 3, open-label trial in HCV and HIV-1 co-infected patients. Patients without cirrhosis received glecaprevir/pibrentasvir 300 mg/120 mg for 8 weeks (without cirrhosis) or 12 weeks (compensated cirrhosis) (n=153).[214,215] Treatment-naïve (any genotype) or treatment-experienced (IFN-based therapy with or without sofosbuvir or sofosbuvir plus ribavirin; excluding genotype 3) patients could be included, although no patients from genotype 5 were enrolled in the study. The primary endpoint was the SVR12, which occurred in 98% (95% CI, 95.8 to 100) of patients.

EXPEDITION-8 was a phase 3b, open-label trial that included a total of 343 treatment-naïve adults with chronic HCV (any genotype) and compensated cirrhosis. Patients received glecaprevir/pibrentasvir 300 mg/120 mg once daily for 8 weeks.[216] Overall SVR12 was 98%. The lowest SVR12 across the genotypes was 95% for genotype 3, including 1 patient that experienced virologic relapse. SVR12 for genotype 5 was 100%; however, there was only 1 patient in this cohort.

SURVEYOR-2 Part 3 was an open-label, randomized trial in treatment-naïve and PRS treatment-experienced subjects with genotype 3 infection without cirrhosis to 12- or 16-weeks of treatment.[217] Patients who are non-cirrhotic received glecaprevir/pibrentasvir 300 mg/120 mg administered daily for 12 or 16 weeks. Patients with compensated cirrhosis were further randomized into 2 treatment arms, 12-weeks (treatment-naïve only) and 16-weeks (PRS treatment-experienced only). SVR12 rate was 95%, 98%, and 96% in the non-cirrhotic, treatment-naïve with compensated cirrhosis, and treatment-experienced with compensated cirrhosis arms, respectively.

MAGELLAN-2 was a phase 3, single-arm, open-label trial that assessed the efficacy of glecaprevir/pibrentasvir for the treatment of HCV in patients who had received a liver or kidney transplant at least 3 months prior (n=100; 80 liver, 20 kidney). [218,219] Noncirrhotic treatment-naive (any genotype) or treatment-experienced (genotypes 1, 2, 4 or 6 with IFN-based therapy with or without sofosbuvir or sofosbuvir plus ribavirin) were assigned glecaprevir/pibrentasvir 300 mg/120 mg once daily for 12 weeks. The primary endpoint was SVR12, which was compared to a historic SVR12 using standard of care. Safety of glecaprevir/pibrentasvir was assessed. Most included patients were infected with

genotype 1 (57%) or genotype 3 (24%). The overall SVR12 was 98% (95% CI, 95.3 to 100) in the experimental group versus 94% in the historical control.

DORA (part 1) was a nonrandomized, open-label, multicenter trial evaluating the efficacy of glecaprevir/pibrentasvir in 47 patients ages 12 to 17 years old with genotypes 1, 2, 3, or 4.[220] Patients with decompensated cirrhosis (Child-Pugh B/C) or HBV co-infection were excluded from the trial. A total of 36 patients were treatment-naïve and 11 were treatment-experienced with an interferon based regimen. The primary efficacy endpoint was the proportion of patients who achieved an SVR12 defined as an HCV RNA > 15 IU/mL at posttreatment week 12. The overall SVR rate was 100% (47/47). The safety and tolerability profile was consistent with the safety profile established for adults.

glecaprevir/pibrentasvir (Mavyret) in genotypes 1, 2, 3, and 4 treatment-naïve and treatment-experienced patients without cirrhosis: pediatric patients ages 3 to 12 years of age

DORA (Part 1 and 2): The efficacy and safety of glecaprevir/pibrentasvir (Mavyret) were studied in 2 open-label phase 2/3 clinical trials.[221] DORA Part 1 included 47 patients ages 12 years to < 18 years old without cirrhosis treated for 8 or 16 weeks and DORA Part 2 evaluated 80 patients ages 3 to < 12 years old over 8, 12, or 16 weeks. In DORA Part 1, data were consistent with that observed in clinical trials in adults. In DORA Part 2, 62 of 80 pediatric patients ages 3 to ≤ 12 years of age without cirrhosis received the weight-based recommended dosage and were included in DORA Part 2 efficacy analysis. Patient types included genotype 1 (73%), genotype 2 (3%), genotype 3 (23%), genotype 4 (3%), treatment naïve (97.5%), treatment-experienced to interferon (2.5%), and HIV-coinfection (1%). The primary endpoint across all clinical trials was SVR12 and the overall SVR12 rate for patients ages 3 to 12 years of age was 98.4% with 1 patient discontinuing treatment due to an adverse event. Adverse events in patients ages 3 to ≤ 12 years were consistent with those observed in adults, with the exception of vomiting (8%), rash (4%), and upper abdominal pain (4%). Other adverse events include fatigue (8%) and headache (8%). One patient discontinued treatment due to grade 3 erythematous rash.

ledipasvir/sofosbuvir (Harvoni) in genotype 1 infection

ION-1: This was a phase 3, randomized, open-label, multicenter trial involving previously untreated patients (n=865) with chronic HCV genotype 1 infection.[222] Patients were randomly assigned in a 1:1:1:1 ratio to receive a fixed-dose combination tablet containing 90 mg of ledipasvir and 400 mg of sofosbuvir once daily for 12 weeks or 24 weeks with or without twice-daily ribavirin, for both treatment durations. Randomization was stratified according to HCV subtype (1a or 1b) and the presence or absence of cirrhosis. The presence of cirrhosis was defined as a liver-biopsy specimen showing evidence of cirrhosis (Metavir stage F4) or Ishak score of 5 or 6, a FibroScan score of more than 12.5kPa or a FibroTest score of more than 0.75 and an aspartate aminotransferase: platelet ratio index of more than 2. Overall, 16% of the 865 patients who received treatment in this trial had cirrhosis. The primary efficacy endpoint was SVR at 12 weeks. The SVR rates for the 4 groups were 99% (95% CI, 96 to 100) for the 12 weeks of ledipasvir/sofosbuvir, 97% (95% CI, 94 to 99) for the 12 weeks of ledipasvir/sofosbuvir plus ribavirin, 98% (95% CI, 95 to 99) for the 24 weeks of ledipasvir/sofosbuvir, and 99% (95% CI, 97 to 100) for the 24 weeks of ledipasvir/sofosbuvir plus ribavirin. The SVR rates for all 4 treatment groups were statistically superior to the calculated historical SVR rate of 60% in this patient population (p<0.001 for all comparisons). The SVR ranged from 94% to 100% in patients with cirrhosis, from 97% to 99% in patients with HCV genotype 1a infection, 97% to 99% among those with a non-CC *IL28B* allele, and 91% to 100% among African

American patients. A total of 10 patients in the two 24-week groups discontinued treatment prematurely due to adverse events and all 10 of these patients achieved SVR; the shortest duration of therapy among these patients was 8 weeks. No patient in the 12-week groups discontinued treatment early. Serious adverse events included cellulitis, chest pain, gastroenteritis, hand fracture, noncardiac chest pain, and pneumonia; each of these occurred in 2 patients. The most common mild to moderate adverse events were fatigue, nausea, headache, and insomnia. The authors concluded the addition of ribavirin did not improve treatment outcomes and the rates of treatment discontinuation were higher in the groups treated for 24 weeks than in the groups treated for 12 weeks. Based on these findings, the regimen of 12 weeks of ledipasvir/ribavirin without ribavirin constitutes an effective treatment for previously untreated patients with HCV genotype 1 infection with or without cirrhosis and is associated with the lowest rate of adverse events of the 4 regimens evaluated.

ION-2: This was a phase 3, randomized, open-label, multicenter study involving patients (n=440) infected with chronic HCV genotype 1 who had not had a SVR after treatment with peginterferon and ribavirin, with or without a protease inhibitor.[223] The 1:1:1:1 randomization arms were identical to ION-1 with 4 total groups, two 12-week treatment groups, 1 with and 1 without added ribavirin and two 24-week treatment groups, 1 with and 1 without added ribavirin. Patients were stratified according to genotype (1a or 1b), presence or absence of cirrhosis, and response to prior therapy (relapse or virologic breakthrough versus no response). These stratification groups were generally balanced among the 4 treatment arms. Overall, 52% of the enrolled patients had received prior treatment with a protease inhibitor regimen and 88% had the non-CC *IL28B* genotype. The primary efficacy endpoint was SVR12 with a secondary endpoint of SVR24. The SVR rates for the 4 groups were 94% (95% CI, 87 to 97), for the 12 weeks of ledipasvir/sofosbuvir, 96% (95% CI, 91 to 99) for the 12 weeks of ledipasvir/sofosbuvir plus ribavirin, 99% (95% CI, 95 to 100) for the 24 weeks of ledipasvir/sofosbuvir, and 99% (95% CI, 95 to 100) for the for the 24 weeks of ledipasvir/sofosbuvir plus ribavirin. The sustained virologic response was superior to the adjusted historical response rate of 25% in this patient population ($p<0.001$ for all comparisons). A total of 11 patients who were on 1 of the 12-week treatment arms experienced virologic relapse. No patient in the group that received 24 weeks of treatment had a virologic relapse. All patients who had achieved an SVR12 also had an SVR24; no patient had a relapse after post-treatment week 12. The response rates were similar among patients with genotype 1a and those with genotype 1b infection, among patients who had previously received peginterferon and ribavirin and those who had received a protease inhibitor regimen, and among those patients with no response to prior treatment and those with prior virologic breakthrough or relapse. Ribavirin had no effect on response rates, regardless of treatment duration. Patients with cirrhosis who received the 12-week regimen, with or without ribavirin, had a SVR rate of 86% and 82%, respectively. The SVR rates for cirrhotic patients randomized to the two 24-week arms were 95% and 100%. The difference between the response rate among patients with cirrhosis who received 12 weeks of treatment and the rates among patients with cirrhosis who received 24 weeks of treatment was significant ($p=0.007$). The multivariate exact logistic-regression analysis identified the absence of cirrhosis as the only baseline factor associated with a significant increase in the rate of response. None of the patients in the study discontinued treatment prematurely due to adverse effects. No serious adverse events occurred in patients who received either 12-week regimen, whereas 6% of patients who received a 24-week therapy experienced a serious adverse event. These serious adverse effects included 1 patient each with hepatic encephalopathy, intervertebral disk protrusion, noncardiac chest pain, spondylolisthesis, convulsion, upper gastrointestinal hemorrhage, and unstable angina. Overall, the rate of adverse events was substantially lower in the group that received 12 weeks

of ledipasvir/sofosbuvir alone (67%) than in the other 3 treatment groups (81% to 90%). Higher rates of constitutional and neuropsychiatric side effects were observed in the 2 groups that received the ribavirin-containing regimen than in the 2 groups that received ledipasvir-sofosbuvir alone.

ION-3: This was a phase 3, randomized, open-label, multicenter trial enrolling previously untreated patients (n=647) with HCV genotype 1 infection without cirrhosis to receive ledipasvir/sofosbuvir for 8 weeks, ledipasvir/sofosbuvir plus ribavirin for 8 weeks, or ledipasvir/sofosbuvir for 12 weeks.[224] Patients were randomized 1:1:1 into these groups and stratified by HCV genotype (1a or 1b). The goal of the trial was to establish the feasibility of shortening the treatment duration for this select group of patients and the primary endpoint was SVR12 as compared to the historical control rate of 60% in this population. A key secondary endpoint was the noninferiority of 8 weeks of ledipasvir/sofosbuvir to the other treatment regimens. Patients eligible for this trial were required to have an HCV RNA level of at least 10^4 IU/mL, alanine and aspartate aminotransferase levels of no more than 10 times the upper limit of normal, a platelet count of more than 90,000 per cubic millimeter, and hemoglobin of at least 11 g/dL in women or at least 12 g/dL in men. The primary endpoint was met in all 3 treatment groups, with SVR rates superior to the adjusted historical control rate of 60% ($p<0.001$ for all comparisons). The 8-week ledipasvir/sofosbuvir treatment arm had a 94% SVR12 rate (95% CI, 90 to 97), the ledipasvir/sofosbuvir/ribavirin 8-week treatment arm had a 93% SVR12 rate (95% CI, 89 to 96), and the 12-week ledipasvir/sofosbuvir arm had a 95% SVR 12 rate (95% CI, 92 to 98). In the secondary analysis of noninferiority, the rate of sustained virologic response among patients who received 8 weeks of ledipasvir/sofosbuvir without ribavirin met the prespecified criteria for noninferiority compared to the response rates in the other 2 treatment groups. Patients with characteristics historically associated with a poor response to interferon-based treatment including non-CC *IL28B* genotype, high viral load at baseline, black race, and HCV genotype 1a infection, had SVR12 rates similar to the rates among patients without these characteristics. The rates of response to 8 weeks of ledipasvir/sofosbuvir ranged from 89% to 100% in all these subgroups. The baseline fibrosis score also had no discernible effect on the SVR12 rate. Five percent of patients in the 8-week ledipasvir/sofosbuvir group experienced a virologic relapse after the end of therapy, as did 4% in the 8-week ledipasvir/sofosbuvir/ribavirin group and 1% in the 12-week group. Fatigue, headache, and nausea were the most common adverse events. Although relapse was more common among patients who received 8 weeks of treatment than those who received 12 weeks of treatment, the small numbers of patients who had a relapse were not sufficient to identify baseline characteristics or response variables during treatment that were associated with relapse. Overall, this study supports the efficacy of an 8-week course of ledipasvir/sofosbuvir across a broad range of previously untreated patients with HCV genotype 1 infection without cirrhosis; however, this regimen has not been evaluated in patients with cirrhosis.

ledipasvir/sofosbuvir (Harvoni) in pediatric patients with genotype 1

The efficacy of ledipasvir/sofosbuvir was evaluated in patients ≥ 12 years of age with HCV genotype 1 without cirrhosis or with compensated cirrhosis in an open-label trial which included a total of 100 patients who were treatment-naïve (n=80) and treatment-experienced (n=20). Patients enrolled in the trial received 12 weeks of treatment with ledipasvir/sofosbuvir once daily. Of the 100 treated patients, age ranged from 12 to 17 years (median, 15 years), weight ranged from 33 to 126 kg (mean, 61 kg), 55% had baseline HCV RNA levels ≥ 800,000 IU/mL, 81% had genotype 1a HCV infection, and 76% had non-CC IL28B alleles (CT or TT). One subject had known compensated cirrhosis. The SVR12 rate was 98% overall (98% [78/80] in treatment-naïve patients and 100% [20/20] in treatment-experienced patients).

None of the subjects experienced on-treatment virologic failure or relapse, and 2 subjects were lost to follow-up.

ombitasvir/paritaprevir/ritonavir and dasabuvir (Viekira Pak) plus ribavirin versus placebo in genotype 1

SAPPHIRE-I was an international phase 3, randomized, double-blind, placebo-controlled trial involving 631 previously untreated patients with HCV genotype 1 infection.[225] Patients were randomized to active treatment with ABT-450/r (150 mg/100 mg) plus ombitasvir (25 mg), dasabuvir (250 mg twice daily) and ribavirin (weight-based dosing), or matching placebos for 12 weeks. Randomization was stratified by HCV genotype (1a or non-1a) and IL28B genotype (CC or non-CC). (After the double-blind period, patients randomized to placebo received the active regimen as open-label therapy for 12 additional weeks). The primary endpoint was SVR12 (HCV RNA < 25 IU/mL at 12 weeks after the end of treatment). The SVR12 of the active treatment group was compared to a historical response rate of 78% in previously untreated patients without cirrhosis who received telaprevir/peginterferon/ ribavirin. The SVR12 of the active treatment group was 96.2% (95% CI, 94.5 to 97.9), which was statistically superior to the historical control. The response rates were 95.3% among patients with HCV genotype 1a and 98% among patients with HCV genotype 1b infections. The SVR12 rates were similar regardless of baseline fibrosis score (97% for F0/F1, 94.3% for F2, and 92.5% for F3). One patient in the active treatment group had virologic failure during the double-blind treatment period and 7 active treatment patients (1.5%) had a relapse by post-treatment week 12. Each of these 8 patients had at least 1 amino acid variant known to confer resistance to 1 of the 3 direct acting antiviral agents included in the regimen. Modifications of the ribavirin dose due to adverse events occurred in 26 patients. The SVR 12 was 93.5% among patients who had a modification of the ribavirin dose and 96.4% among those who did not have a ribavirin dose modification. Nausea, pruritus, insomnia, diarrhea, and asthenia occurred in significantly more patients receiving active treatment compared to patients receiving placebo ($p<0.05$ for all comparisons).

ombitasvir/paritaprevir/ritonavir and dasabuvir (Viekira Pak) plus ribavirin in genotype 1 patients with previous treatment experience

SAPPHIRE-II was an international, randomized, placebo-controlled, double-blind, phase 3 trial with an identical study design to SAPPHIRE-I but enrolled patients (n=394) who had previously been treated with peginterferon-ribavirin (PEG/RBV) and had a partial response or a null response or had experienced a relapse.[226] All patients had HCV genotype 1 and no cirrhosis. Patients were excluded if they did not have a response to prior triple therapy including a protease inhibitor. Patients with Metavir scores of 3 or above were also excluded. The historical response rate for this group of patients was determined to be 65% based on a retreatment regimen of peginterferon-ribavirin and telaprevir. The SVR12 for the active treatment group in this trial was 96.3% (95% CI, 94.2 to 98.4), superior to the historical control rate. Response rates of 95.3%, 100%, and 95.2% were seen in patients with a prior relapse, a prior partial response, and a prior null response, respectively. The 2 most common adverse events in both the active treatment group and the placebo group were headache and fatigue. Only pruritus occurred more frequently in the active regimen group compared to placebo (13.8% versus 5.2%; p=0.03). A total of 2.4% of patients who completed therapy had a post-treatment viral relapse.

ombitasvir/paritaprevir/ritonavir and dasabuvir (Viekira Pak) with or without ribavirin in genotype 1

PEARL II was a multicenter, open-label, phase 3 trial designed to answer the question of whether ribavirin is necessary in the ombitasvir/paritaprevir/ritonavir plus dasabuvir regimen in the treatment of patients with HCV genotype 1b without cirrhosis who had previously been treated with peginterferon and ribavirin (PEG/RBV).[227] Patients (n=186) were randomized to identical regimens of co-formulated ombitasvir/paritaprevir/ritonavir (150 mg/100 mg/25 mg) and dasabuvir (250 mg twice daily), with or without ribavirin (weight-based dosing), for 12 weeks. Previous null responders, partial responders, and relapsers were evenly stratified between the 2 treatment arms. The primary endpoint was SVR12, which was compared to a historical response rate of 64% in this patient population treated with peginterferon, ribavirin, and telaprevir. Hemoglobin levels less than the lower limit of normal at the end of treatment was a secondary endpoint. The SVR12 rate for the group of patients who received ribavirin was 96.6% (95% CI, 92.8 to 100) and 100% for the group of patients who did not receive ribavirin (95% CI, 95.9 to 100). The rate of response in the group who did not receive ribavirin was non-inferior to the group who did receive ribavirin and both groups were non-inferior to the historical response rate. In the group of patients receiving ribavirin, SVR12 rates were 93.5%, 96%, and 100% in prior null responders, partial responders, and relapsed patients, respectively. SVR12 rates were 100% in all subgroups of the ribavirin-free arm. The most common adverse events in both groups were fatigue (31.9% and 15.8%) and headache (24.2% and 23.2%) in the ribavirin and non-ribavirin groups, respectively. Patients receiving ribavirin also experienced statistically significant higher rates of insomnia, anemia, rash, and increased bilirubin levels. Hemoglobin level less than the lower limit of normal at the end of treatment was experienced more often by patients receiving ribavirin than those who did not receive ribavirin (42% versus 5.5%, respectively; $p<0.001$).

Two phase 3, double-blind, randomized, placebo-controlled trials were designed to evaluate the role of ribavirin in treatment-naive HCV genotype 1 patients without cirrhosis (PEARL-III and PEARL-IV).[228] The safety and efficacy of a 12-week treatment regimen of co-formulated ABT-450/r-ombitasvir (150 mg/100 mg/25 mg) and dasabuvir (250 mg twice daily), with or without ribavirin (weight-based dosing), were examined in previously untreated patients without cirrhosis who had HCV genotype 1a (PEARL-IV) or HCV genotype 1b (PEARL-III). Patients in both trials received identical open-label regimens of ABT-450/r-ombitasvir and dasabuvir along with either ribavirin or placebo. In PEARL-III, 419 patients underwent randomization and, in PEARL-IV, 305 patients underwent randomization. SVR12 was the primary endpoint for all analyzed groups and the primary objective of both studies was to assess the noninferiority of all groups compared to a corresponding historical rate (72% for HCV genotype 1a and 80% for HCV genotype 1b). The secondary efficacy objective in each study was noninferiority of the SVR12 rate in the group that did not receive ribavirin as compared with the group that did receive ribavirin. Other objectives included assessing the percentage of patients in each group with a hemoglobin level below the lower limit of normal at the end of treatment and the percentage of patients in each group with virologic failure during treatment or relapse after treatment. For patients with HCV genotype 1b (PEARL-III), 99.5% (95% CI, 98.6 to 100) of patients receiving ribavirin achieved an SVR12 and 99% (95 % CI, 97.7 to 100) of patients who did not receive ribavirin achieved an SVR12. Among the patients with HCV genotype 1a (PEARL-IV), 97% (95% CI, 93.7 to 100) of patients receiving ribavirin achieved an SVR12 and 90.2% (95% CI, 86.2 to 94.3) of patients who did not receive ribavirin achieved an SVR12.

The SVR12 rates for both genotype 1a regimens (with or without ribavirin) were non-inferior and superior to the historical rate; however, the regimen without ribavirin for genotype 1a patients did not meet the non-inferiority criteria as compared to the regimen with ribavirin and there was a statistically significant difference between these 2 groups (95% CI, -12 to -1.5). The rate of virologic failure was higher in the HCV genotype 1a patients who did not receive ribavirin (7.8%) compared to the HCV genotype 1a group who did receive ribavirin (2%). A total of 18 patients with genotype 1a infection had virologic failure, 16 of whom received the regimen without ribavirin. For genotype 1b patients, the SVR12 rates among patients who received ribavirin and those who did not were both non-inferior and superior to the historical control. In addition, the SVR12 rate among patients who did not receive ribavirin was non-inferior to the rate among those who received ribavirin (difference -0.5 percentage points [95% CI, -2.1 to 1.1] for genotype 1b patients. In both studies, adverse events were more frequently reported in the groups receiving antiviral regimens that contained ribavirin than in groups that received the ribavirin-free regimen (p=0.03 in the genotype 1a study and p=0.003 in the genotype 1b study). The most common adverse events reported in the 2 studies, headache and fatigue, did not differ significantly in either study between the group that received ribavirin and the group that did not receive it. Pruritus, nausea, and insomnia all occurred at a higher frequency among patients who received ribavirin than among those who did not. In the genotype 1a study, 42% of patients treated with ribavirin had a hemoglobin level below the lower limit of normal at the end of treatment compared to only 3.9% of patients who received the ribavirin-free regimen (p<0.001). Similarly, in the genotype 1b study, 51.2% of patients who received ribavirin had a low hemoglobin level at the end of treatment as compared with 3.4% of patients who did not receive ribavirin (p<0.001).

ombitasvir/paritaprevir/ritonavir and dasabuvir (Viekira Pak) plus ribavirin in genotype 1 patients with compensated cirrhosis

TURQUOISE-II was a randomized, open-label, international phase 3 trial enrolling both untreated and previously treated adults (n=380) with HCV genotype 1 infection and compensated cirrhosis (CC).[229] Eligible patients had documentation of liver cirrhosis, as well as a plasma HCV RNA level of more than 10,000 IU/mL. Patients enrolled in the trial also were required to have a baseline platelet count of at least 60,000 mm^3, a serum albumin of ≥ 2.8 g/dL, a total bilirubin < 3 g/dL, an INR of 2.3 or less, and a serum alpha-fetoprotein level of 100 ng/mL or less. Patients who had previously received telaprevir or boceprevir were excluded from the study, as were patients with a diagnosis of hepatocellular carcinoma. All patients received ABT-450 with ritonavir (ABT-450/r) at a dose of 150 mg of ABT-450 and 100 mg of ritonavir and ombitasvir 25 mg co-formulated into 1 tablet once daily along with dasabuvir 250 mg twice daily and ribavirin administered at 1,000 mg or 1,200 mg twice daily according to body weight. Patients were randomized to either 12 weeks of therapy or 24 weeks of therapy. Patients were stratified according to HCV subgenotype (1a or 1b), IL28B genotype (CC or non-CC) and whether or not they had failed previous PEG/RBV as well as the type of failure (null response, partial response, or relapse). The primary efficacy endpoint was SVR12 compared to a historical rate of 47% (95% CI, 41 to 54) with a regimen of peginterferon/ribavirin/telaprevir in this patient population. A total of 191 of 208, or 91.8%, (97.5% CI, 87.6 to 96.1) of patients who were randomized to 12 weeks of treatment achieved a SVR12, while 95.9% (97.5% CI, 92.6 to 99.3) of patients who were randomized to 24 weeks of treatment achieved a SVR12. In both treatment groups and across the randomization strata, the primary endpoint of superiority compared to the historical SVR12 rate with telaprevir-based regimens was achieved. The difference in SVR12 between the 12-week treatment group and the 24-week treatment group was not

significant (p=0.09); however, a multivariate logistic-regression analysis indicated that a prior null response to peginterferon-ribavirin, infection with HCV subgenotype 1a, and former injection-drug use were associated with a lower likelihood of achieving SVR12. This population had an SVR12 rate of 80% in the 12-week arm and 92.9% in the 24-week arm. When examining virologic failure during treatment or relapse after treatment, significantly more patients in the 12-week group than in the 24-week group had a relapse (5.9% [95 % CI, 2.7 to 9.2] versus 0.6% [95% CI, 0 to 1.8]). More than half of the relapses in the 12-week group occurred in patients with HCV genotype 1a and a prior null response to peginterferon-ribavirin treatment. The majority of adverse events were mild or moderate in severity. Two percent of patients in either randomized group discontinued the study drug due to an adverse event. The most frequent grade 3 laboratory abnormality was elevated total bilirubin levels. There were 34 patients who required a reduction in the ribavirin dose due to anemia; all 34 of those patients achieved SVR12.

ombitasvir/paritaprevir/ritonavir and dasabuvir (Viekira Pak) plus ribavirin in HCV/HIV coinfected patients with genotype 1

TURQUOISE-I was an open-label clinical trial involving 63 patients with HCV/HIV coinfection.[230] Patients in this trial were treated for 12 or 24 weeks with Viekira Pak in combination with ribavirin and were on a stable HIV antiretroviral therapy regimen. Antiretroviral medications were adjusted according to protocol stipulations depending on the drug regimen. Of the patients enrolled in the trial, 67% were HCV treatment-naïve, 19% had compensated cirrhosis, and 89% had HCV genotype 1a infection. The SVR12 rates were 91% (51/56 patients) in those patients with HCV genotype 1a infection and 100% (7/7) for patients with HCV genotype 1b infection. One patient had confirmed HIV-1 RNA > 400 copies/mL during the post-treatment period but had no evidence of resistance to the antiretroviral drug regimen. No subjects switched their antiretroviral regimen due to loss of plasma HIV-1 RNA suppression.

sofosbuvir (Sovaldi) and ribavirin in adults with genotypes 2 and 3

POSITRON: This randomized, double-blinded, placebo-controlled study evaluated sofosbuvir in patients with genotypes 2 and 3 that were interferon intolerant as demonstrated during a prior course of treatment, interferon ineligible due to medical history, or unwilling to take interferon.[231] Most patients had no prior HCV treatment (81%). A total of 278 patients were administered dual therapy of sofosbuvir plus ribavirin or placebo for 12 weeks. Study drug was superior to placebo with an SVR12 rate of 78% versus 0% for placebo. In the study drug arm, higher SVR12 rates were reported in patients with genotype 2 compared to those with genotype 3 (93% versus 61%, p<0.0001). In addition, patients without cirrhosis had higher SVR12 compared to those with cirrhosis (81% versus 61%). The overall relapse rate was 20%, 5% of patients with genotype 2 relapsed, and 38% with genotype 3. No virologic resistance was detected in patients who did not have a sustained virologic response.

FUSION: This randomized, double-blinded, active-controlled study evaluated dual therapy, sofosbuvir plus ribavirin, for 12 or 16 weeks in 201 treatment-experienced patients with genotypes 2 and 3.[232] Approximately 25% of subjects had prior nonresponse to an interferon-based regimen, and 75% had prior relapse or breakthrough. The SVR12 rate was 50% in the 12-week group and 71% in the 16-week group, this difference was statistically significant. In both treatment groups, subjects with genotype 2 had higher SVR12 rates compared to genotype 3. Extending the treatment duration by 4 weeks resulted in an increased SVR12 rate for genotype 2 from 82% to 89%, and for genotype 3 from 30% to 62%. Relapse rate for genotype 2 was 18% and 11%, for 12 versus 16 weeks of therapy, respectively; relapse

rate for genotype 3 was 66% and 38%, for 12 versus 16 weeks of therapy, respectively. Presence of cirrhosis was associated with a decreased rate of SVR. No virologic resistance was detected in patients who did not have a sustained virologic response.

FISSION: This randomized, open-label, active-controlled trial enrolled 499 treatment-naïve patients to evaluate dual therapy of sofosbuvir plus weight-based ribavirin for 12 weeks compared to peginterferon 180 mcg/week plus ribavirin 800 mg per day for 24 weeks for the treatment of HCV genotype 2 and 3.[233] The overall SVR12 rate was 67% in each treatment group; for those with genotype 2, 95% achieved SVR12 with sofosbuvir plus ribavirin, and 78% achieved SVR 12 with peginterferon plus ribavirin; for those with genotype 3, 56% achieved SVR12 with sofosbuvir plus ribavirin and 63% achieved SVR12 with peginterferon plus ribavirin. Greater relapse rate was seen for genotype 3, compared to genotype 2, regardless of treatment regimen. No drug-resistance was detected in the 74 patients that relapsed. With the exception of dizziness and anemia, all events occurring in at least 10% of patients were more common among patients receiving peginterferon than among those receiving sofosbuvir.

sofosbuvir (Sovaldi) plus ribavirin in pediatric patients with genotype 2 or 3

The efficacy of sofosbuvir plus ribavirin in pediatric patients ≥ 12 years of age was evaluated in a phase 2, open label clinical trial of 50 subjects with HCV genotype 2 (n=13) or genotype 3 (n=37).[234] Patients in the trial with genotype 2 were treated with sofosbuvir plus weight-based ribavirin for 12 weeks and patients with genotype 3 were treated with the same combination for a total of 24 weeks. The patients in the trial ranged from 12 to 17 years of age, with a median age of 15 years. Weight ranged from 30 to 101 kg, with an average weight of 61 kg. Other baseline characteristics included: 18% were treatment-experienced, 66% had baseline HCV RNA levels ≥ 800,000 IU/mL, 74% had non-CC IL28B alleles (CT or TT), and no subjects had known cirrhosis. The SVR12 rate for patients with genotype 2 was 100% (13/13) and SVR12 was 97% (36/37) in genotype 3 subjects. No subject experienced on-treatment virologic failure or relapse.

sofosbuvir (Sovaldi) and ribavirin in genotype 1 (treatment-naïve), 2 or 3 (treatment-naïve and experienced) HCV/HIV-1 coinfections

PHOTON-1:[235] This was an open-label, phase 3, clinical trial evaluating 12 or 24 weeks of treatment with sofosbuvir and ribavirin in patients with genotype 1 (treatment-naïve), genotype 2 or 3 (treatment-naïve and experienced) HCV coinfected with HIV-1. Patients received 400 mg sofosbuvir and weight-based ribavirin daily for 12 or 24 weeks based on genotype and prior treatment history. Patients were either not on antiretroviral therapy with a CD4+ cell count >500 cells/mm^3 or had virologically suppressed HIV-1 with a CD4+ cell count >200 cells/mm^3. Efficacy data for 210 patients are reported. In the trial, 76% (95% confidence interval [CI], 67 to 84) of genotype 1 HCV treatment-naïve patients receiving 24 weeks of therapy achieved a SVR 12. SVR12 for genotypes 2 and 3 was 88 (95% CI, 70 to 98) and 67% (95% CI, 51 to 80), respectively. All patients in the study who did not achieve SVR12 had viral relapse after cessation of therapy, with the exception of 2 participants who were non-adherent to study drugs.

sofosbuvir/velpatasvir (Epclusa) in genotypes 1, 2, 4, 5, and 6

ASTRAL-1: This randomized double-blind trial evaluated the efficacy of sofosbuvir/velpatasvir in treatment-naïve and treatment-experienced (prior interferon-containing regimen) patients (n=740) with genotype 1, 2, 4, 5, or 6 without cirrhosis or with compensated cirrhosis (Child-Pugh A).[236] Patients were randomized 5:1 to either sofosbuvir/velpatasvir 400/100 mg or placebo once daily for 12 weeks;

however, all patients with genotype 5 were assigned sofosbuvir/velpatasvir due to the low prevalence of this genotype. In this trial, randomization was stratified according to the genotype and the presence or absence of cirrhosis. In the sofosbuvir/velpatasvir group (n=624), 34% of the patients had HCV genotype 1a, 19% genotype 1b, 17% genotype 2, 19% genotype 4, 6% genotype 5, and 7% genotype 6. Nineteen percent of the patients assigned sofosbuvir/velpatasvir had cirrhosis. The primary efficacy endpoint was the rate of SVR12. Overall, SVR12 among patients who received 12 weeks of sofosbuvir/velpatasvir was 99% (95% CI, 98 to > 99), which was significantly superior to the prespecified performance goal of 85% (p<0.0001). None of the 116 patients in the placebo group achieved SVR. Rates of SVR were similar regardless of the HCV genotype: 98% in patients with genotype 1a infection, 99% with genotype 1b, 100% with genotype 2, 100% with genotype 4, 97% with genotype 5, and 100% with genotype 6. Nearly all of the patients with cirrhosis achieved SVR12 (all genotypes; 120/121; 99%). Only 1 of the patients in the sofosbuvir/velpatasvir group discontinued treatment prematurely because of an adverse event.

sofosbuvir/velpatasvir (Epclusa) in genotype 2

ASTRAL-2: This open-label trial (n=266) compared sofosbuvir/velpatasvir 400/100 mg once daily (n=134) to sofosbuvir 400 mg with weight-based ribavirin for 12 weeks (n=132) in treatment-naïve and treatment-experienced (prior interferon-containing regimen) patients with genotype 2.[237] Fourteen percent of those enrolled had cirrhosis while 15% were treatment-experienced. The overall SVR12 rates (the primary outcome) in subjects who received sofosbuvir/velpatasvir and sofosbuvir with ribavirin were 99% (95% CI, 96 to 100) and 94% (95% CI, 88 to 97), respectively. There were no virologic failures among patients receiving sofosbuvir/velpatasvir despite the presence of NS5A and NS5B resistance-associated variants; however, in those receiving sofosbuvir with ribavirin, 6 patients (5%) had a virologic relapse and 2 were lost to follow-up.

sofosbuvir/velpatasvir (Epclusa) in genotype 3

ASTRAL-3: This open-label trial (n=552) compared sofosbuvir/velpatasvir 400/100 mg once daily for 12 weeks (n=277) to sofosbuvir 400 mg with weight-based ribavirin for 24 weeks (n=275) in treatment-naïve and treatment-experienced (prior interferon-containing regimen) patients with genotype 3.[238] Thirty percent of those enrolled had cirrhosis while 26% were treatment-experienced. The SVR12 rates in patients who received sofosbuvir/velpatasvir were 95% (95% CI, 92 to 98) compared to 80% (95% CI, 75 to 85) in those who received sofosbuvir with ribavirin.

sofosbuvir/velpatasvir (Epclusa) in genotypes 1, 2, 3, 4, and 6 with decompensated cirrhosis

ASTRAL-4: An open-label trial, evaluated the efficacy of sofosbuvir/velpatasvir in 267 treatment-naïve and treatment-experienced patients with genotypes 1 through 6 chronic HCV infection and decompensated cirrhosis (Child-Pugh B).[239] Patients were randomized 1:1:1 to sofosbuvir/velpatasvir 400/100 mg once daily for 12 weeks, sofosbuvir/velpatasvir 400/100 mg once daily with ribavirin for 12 weeks, or sofosbuvir/velpatasvir 400/100 mg once daily for 24 weeks. Of those who received treatment, 78% were genotype 1, 4% were genotype 2, 15% were genotype 3, 3% were genotype 4, and < 1% were genotype 6; while not excluded, no genotype 5 patients were enrolled. The median baseline Child-Pugh score was 8 (range, 5 to 10) and the median baseline Model for End-Stage Liver Disease (MELD) score was 10 (range, 6 to 24; majority ≤ 15). Overall SVR12 rates, the primary outcome, were 83% (95% CI, 74

to 90), 94% (95% CI, 87 to 98), and 86% (95% CI, 77 to 92) for the 12-week regimen of sofosbuvir/velpatasvir, the 12-week regimen of sofosbuvir/velpatasvir with ribavirin, and the 24-week regimen of sofosbuvir/velpatasvir, respectively. Notably, SVR12 rates as low as 50% were reported in genotype 3 patients assigned sofosbuvir/velpatasvir for 12 or 24 weeks (no ribavirin).

sofosbuvir/velpatasvir (Epclusa) in genotypes 1, 2, 3, and 4 treatment naïve and treatment-experienced liver transplant patients without cirrhosis or with compensated cirrhosis

Trial 2104: The efficacy of sofosbuvir/velpatasvir in liver transplant patients with HCV was studied in this open label trial with patients who were treatment-naïve or had previously received HCV therapy.[240,241] The trial included 79 patients with genotypes 1 (47%), 2 (4%), 3 (44%), or 4 (5%); 18% had compensated cirrhosis, and 59% were treatment experienced. Patients were allowed to continue their immunosuppressant therapy throughout the trial with tacrolimus (71%), mycophenolic acid (24%), cyclosporine (14%), and azathioprine (11%) being most commonly used. The primary endpoints were SVR12 and discontinuations due to adverse events. The overall SVR12 rate was 96% with 95% of genotype 1 patients, 97% of genotype 3 patients, and 100% of genotypes 2 and 4 patients achieving an SVR. There were 2 patients that experienced virologic relapse; one with genotype 1a infection was non-cirrhotic and treatment naïve, and one with genotype 3 infection was non-cirrhotic and treatment experienced. One patient discontinued treatment due to hyperglycemia.

sofosbuvir/velpatasvir (Epclusa) in genotypes 1, 2, 3, 4, and 6, treatment-naïve or treatment-experienced without cirrhosis or with compensated cirrhosis: pediatric patients ages 3 to 6 years of age

Trial 1143: The efficacy of sofosbuvir/velpatasvir was studied over 12 weeks in pediatric patients 3 years of age and older (n=214) with chronic HCV infection in a phase 2, open-label clinical trial.[242,243] The results of patients ages ≥ 6 years of age were consistent with those observed in adult clinical trials. In ages 3 years to < 6 years of age, the trial included 41 treatment-naïve patients with genotype 1 (78%), 2 (15%), 3 (5%), or 4 (2%), and 49% had baseline HCV RNA levels ≥ 800,000 IU/mL. One of the main outcome measures was SVR12, and the overall SVR12 rate in patients ages 3 years to < 6 years was 83%, with 88% of genotype 1 patients, 50% with genotype 2 patients, and 100% with genotype 3 and 4 patients achieving SVR12. Seven patients discontinued treatment with 5 due to adverse events. Gastrointestinal adverse events were the most commonly reported events in patients < 6 years of age compared with older patients. Mild (grade 1 or 2) adverse events, vomiting, and product use issue (e.g., spitting up the drug) were also reported and resulted in discontinuation in 12% of patients.

sofosbuvir/velpatasvir/voxilaprevir (Vosevi) in genotypes 1, 2, 3, 4, 5, and 6 treatment-experienced patients without cirrhosis or with compensated cirrhosis

POLARIS-1/POLARIS-4: The efficacy of sofosbuvir/velpatasvir/voxilaprevir was studied in 2 placebo-controlled trials (POLARIS-1 and POLARIS-4) in 748 patients.[244,245] POLARIS-1 included patients diagnosed with HCV genotypes 1 through 6 with or without compensated cirrhosis who failed a regimen containing NS5A inhibitors. POLARIS-4 included patients with genotype 1, 2, 3, or 4 with or without compensated cirrhosis who failed a DAA-containing regimen that did not include an NS5A inhibitor. Both trials were 12 weeks in duration. In POLARIS-1, patients were blinded and randomized to receive sofosbuvir/velpatasvir/voxilaprevir or placebo. In POLARIS-4, patients were randomized to receive

sofosbuvir/velpatasvir/voxilaprevir or sofosbuvir/velpatasvir in an open-label fashion. All doses were administered once-daily by mouth in these trials. The primary endpoint for both trials was the proportion of patients who achieved SVR12, defined as HCV RNA less than lower limit of quantification (LLOQ) at 12 weeks after stopping study treatment. In POLARIS-1, the sofosbuvir/velpatasvir/voxilaprevir group achieved an overall SVR12 of 96% compared to 0% in the placebo group ($p<0.001$). In POLARIS-4, the sofosbuvir/velpatasvir/voxilaprevir arm achieved an overall SVR12 rate of 97% compared to 88% in the sofosbuvir/velpatasvir arm ($p<0.001$). Specifically, in genotypes 1a and 3, the SVR12 rates were 97% and 96% for the sofosbuvir/velpatasvir/voxilaprevir arm compared to 82% and 85% for the sofosbuvir/velpatasvir arm, respectively. In POLARIS-4, sofosbuvir/velpatasvir/voxilaprevir was administered for 12 weeks to 18 HCV genotype 4 subjects, with or without cirrhosis, who had prior exposure to a sofosbuvir-containing regimen without an NS5A inhibitor. All subjects achieved SVR12.

SUMMARY

Therapy for chronic hepatitis C virus (HCV) has evolved substantially in the last few decades since interferon-alpha was first approved for this indication. Genotype 1 accounts for about 70% to 75% of the HCV cases in the US. Historically, monotherapy with interferon resulted in sustained virologic responses (SVR) of approximately 10% to 20% in patients with genotype 1 and was associated with substantial adverse drug effects. With the introduction of pegylated interferons, which prolonged half-life and improved response rate, as well as the addition of ribavirin, the standard of care became dual therapy with peginterferon plus ribavirin. This combination resulted in SVR rates of 40% to 50% and remained the standard of care for many years; however, this regimen was not well tolerated as interferon therapy is associated with significant adverse effects, including influenza-like illness, neuropsychiatric symptoms, and ribavirin is associated with anemia. Triple therapy with the first generation protease inhibitors (no longer available), peginterferon, and ribavirin resulted in SVR rates of 60% to 80% in genotype 1 HCV patients. An additional NS3/4A protease inhibitor, simeprevir (Olysio), was approved in 2013. It is considered a second generation protease inhibitor but has been discontinued. The second wave of protease inhibitors offer some advantages over the first generation NS3/4A protease inhibitors, including improved pharmacokinetics allowing for once daily dosing, possible shorter treatment durations, and a more tolerable side effect profile.

In December 2013, sofosbuvir (Sovaldi) was approved by the FDA with a breakthrough therapy designation. Sofosbuvir represents a new class of direct acting antivirals (DAAs) as an HCV nucleotide analog NS5B polymerase inhibitor. It is indicated as a component of a combination regimen for patients with HCV genotypes 1, 2, 3, and 4, resulting in SVR rates of approximately 90% in treatment-naïve patients. Sofosbuvir (Sovaldi) combined with ribavirin for the treatment of genotypes 2 and 3 represented the first all-oral regimen approved by the FDA for HCV therapy.

In 2014, FDA rulings brought about new therapies and expanded indications for previously approved medications. In October 2014, a new fixed-dose once daily oral combination tablet of ledipasvir/sofosbuvir (Harvoni) was approved for the treatment of HCV genotype 1, and its indication was expanded to include patients with genotypes 4, 5, and 6 in November 2015. This therapy combines ledipasvir, the first in a new class of DAAs classified as an HCV NS5A inhibitor, and sofosbuvir, an HCV nucleotide analog NS5B polymerase inhibitor. In December 2014, the combination ombitasvir/paritaprevir/ritonavir + dasabuvir (Viekira Pak) was approved for the treatment of genotype 1 patients with an extended-release formulation (Viekira XR) released in July 2016, the latter of which

has since been removed from the market. This combination includes an NS5A inhibitor (ombitasvir), an NS3A/4A protease inhibitor (paritaprevir), a non-nucleoside NS5B polymerase inhibitor (dasabuvir), and a CYP3A inhibitor (ritonavir) to boost paritaprevir pharmacologically, thereby resulting in increased plasma concentrations. The therapies approved in 2014 represent significant innovation in the treatment hepatitis C as these all-oral regimens have shown SVR rates of ≥ 90%.

A similar agent, ombitasvir/paritaprevir/ritonavir (Technivie) was approved in 2015 and was indicated for the treatment of genotype 4 in combination with ribavirin in patients without cirrhosis or with compensated cirrhosis and has also demonstrated SVR rates of ≥ 90% in clinical trials. This product has since been discontinued. Daclatasvir (Daklinza), also approved in 2015, was indicated with sofosbuvir for the treatment of genotypes 1 or 3 with SVR rates of ≥ 90% as well, but sustained SVR rates were reduced in patients with cirrhosis and certain genetic polymorphisms. Notably, however, Bristol-Myers Squibb ceased distribution of Daklinza (daclatasvir) in 2019.

Approved in January 2016, elbasvir/grazoprevir (Zepatier) combines a NS5A inhibitor with another NS3A/4A protease inhibitor and is indicated for genotypes 1 and 4 with or without ribavirin. Testing for NS5A resistance-associated polymorphisms is needed for patients with genotype 1a since presence may affect both treatment duration and eligibility for this regimen. In June 2016, the fixed-dose once daily pangenotypic combination of sofosbuvir/velpatasvir (Epclusa) was approved, which introduced the first hepatitis C treatment with activity against all 6 genotypes. In July 2017, the fixed-dose once daily pangenotypic combination of sofosbuvir/velpatasvir/voxilaprevir (Vosevi) was approved as the first therapy indicated for treatment-experienced patients with prior therapy including an NS5A inhibitor or genotype 1a or 3 patients previously treated with sofosbuvir without an NS5A inhibitor. In August 2017, the fixed-dose once daily pangenotypic combination glecaprevir/pibrentasvir (Mavyret) was approved and is indicated for treatment-naïve patients without cirrhosis or with compensated cirrhosis and treatment-experienced patients (genotype 1 patients with prior treatment with NS5A inhibitor without prior NS3/4A PI or NS3/4A PI without prior NS5A inhibitor; genotypes 1, 2, 3, 4, 5, and 6 with prior treatment with interferon, pegylated interferon, ribavirin, and/or sofosbuvir) without cirrhosis or with compensated cirrhosis. This is the first combination with an indication for an 8-week treatment duration in treatment-naïve patients without cirrhosis. Since its original approval, the use of glecaprevir/pibrentasvir as an 8-week regimen has been expanded to include patients with compensated cirrhosis as well.

The American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) has published guidance for testing, managing, and treating hepatitis C. This guidance defines recommended regimens (favored for most patients), alternative regimens (effective regimens that may be optimal for a specific patient situation, though not considered a recommended regimen for most patients due to potential disadvantages, limitations use in select populations, or less supporting data), as well as regimens that are not recommended (clearly inferior or harmful treatment options) for each genotype. The guidelines offer expanded options for patients not addressed in the current FDA labeling including patients who are interferon-ineligible, as well as patients who have not responded to previous standard therapy. The AASLD/IDSA guidelines are continually updated including consideration for advances in treatment and the availability of all-oral regimens with substantially higher SVR rates compared to preceding treatment options.

The HCV market has shown substantial growth in the past few years, including pangenotypic treatment options, salvage therapy, ribavirin-free therapies, and shorter regimens. Furthermore, multiple agents within this class are approved for the treatment of children as young as 3 years of age.

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